American Journal of Obstetrics and Gynecology

VOL. 67 MARCH, 1954 No. 3

Original Communications

DAMAGE TO POSTERITY CAUSED BY IRRADIATION OF THE GONADS*

H. J. MULLER, D.SC.,** BLOOMINGTON, IND.

IT IS an especial privilege to have been invited to sketch out some of the major points in this field. It serves as somewhat of a consolation for the fact that, in 1928, after I had been invited to present my results on this subject to the Texas chapter of the Radiological Society, the invitation was cancelled without explanation just before the meeting. Ignorance of the matter was evidently preferred to controversy. It is because this attitude has persisted to a considerable extent until today that the subject is still considered, in some circles, to be controversial.

To those acquainted with the scientific evidence, the damaging of future generations caused by the application of radiation to the gonads is not a controversial question and has not been so for a quarter of a century. The only question is, how much damage is caused by a given dose?

The main reason so few people outside the field of genetics have realized this situation is because the subject of genetics is not required for a medical degree, even though it is basic for an understanding of life processes in general. At least, geneticists hold that the gene is the basis of life, and that genes stand behind and control the metabolic processes and, in fact, all processes of the organism. It is only in the light of genetic principles, which are simple in their essence although often intricate in their working out, that the validity and significance of the evidence for the production of hereditary damage by irradiation can be elucidated. In doing this, frankness is necessary, if the irrelevance of the published data concerning the presence or absence of such effects in human beings is to be understood.

*Presented at a meeting of the New York Obstetrical Society on Jan. 13, 1953.

**Dr. Muller is Distinguished Service Professor at Indiana University. He received the Nobel Prize in Physiology and Medicine in 1946 for his discovery of the production of mutations by x-rays.

In order that such misunderstanding may be avoided in this and other fields involving genetics, as for instance in the field of blood groups, it would be highly desirable for the readers of this paper to use their influence toward having genetics included among the many—unfortunately, too many—subjects of the medical or premedical curriculum.

The reason why my work on the genetic effects of radiation carried out in 1926 and thereafter has used the fruit fly (Drosophila) as its material is purely because of the suitability of this organism for such experimentation. It is because (as Castle, Moenkhaus, Payne, Lutz, Morgan, Guyénot, and others had long previously shown) so many generations of these flies can be obtained in so short a time, and so many individuals within so small a space, at relatively little cost, while at the same time the breeding can be readily controlled and variations in numerous characteristics can be distinguished. But although I used only fruit flies, the findings concerning the genetic effects of radiation were quickly extended by others to very different organisms. Thus it soon became evident that the production of permanent hereditary changes, i.e., *mutations,* by ionizing radiation is a universal biological phenomenon. It extends with certainty down in the scale of organisms as far as protozoa, bacteria, and even viruses, and across to plants as far as fungi, liverworts, monocotyledons, and dicotyledons. Proceeding up the animal kingdom it extends, among invertebrates, to silkworms and wasps, and, among vertebrates, to mammals, represented by mice.

The most important fallacy concerning mutations which is prevalent among nongeneticists is that they are usually the cause of grave, conspicuous abnormalities, such as circus freaks or monsters. Of course there *are* circus freaks and monsters that are due to mutation but these are very rare unusual mutations indeed, compared with the general run. However, just because these drastic mutations are so easy to recognize they are the very ones which have chiefly been used by geneticists in their studies of hereditary transmission, and also in their textbooks and class material on the subject for students. This has been a justifiable practice for these purposes, inasmuch as very elaborate experiments have shown that the basic principles of inheritance are after all exactly the same for these gross abnormalities as for the far commoner mutations which have effects too small or variable to be recognized. But, in consequence, the erroneous impression has been produced among most nongeneticists that the typical mutant is an obviously aberrant individual. The fact is that for each mutation drastic enough to be recognizable in the first or second generation after it has occurred there are hundreds of others with effects too small or too hidden to be seen.

It must be remembered that, with rare exceptions, a given mutant gene is received by an individual from only one of his parents; that is, he has the gene in what is called the *heterozygous* condition. The corresponding normal gene which he received from his other parent is usually *dominant* to the mutant gene, in that the normal gene exercises much more influence than the mutant one in determining the characteristics of the individual, although recent work has

disclosed the important fact that the mutant gene even when heterozygous does exert some effect. In the course of transmission of a mutant gene through many generations it occasionally happens that two individuals heterozygous for the same mutant gene mate together, producing a child *homozygous* for the mutant gene, that is, provided with the gene from both parents. In that case, the effects of the mutant gene on the given individual are usually much more pronounced than in the heterozygous individuals. Yet most mutant genes even when homozygous have effects which are too small or hidden to be recognizable, especially since they tend to be lost to view in the welter of variation which is being simultaneously caused in the population by differences in environmental conditions as well as in numerous other genes affecting the character in question.

It is also to be observed that most mutant genes which arise and are inherited never have an opportunity to meet their like in fertilization and therefore fail to attain the homozygous condition. This is because any given mutant gene is so rare in the population, in most cases, that it would usually have to be transmitted through hundreds of generations before two germ cells, both of which contained a representative of this same mutant gene, happened to unite. Before that time, the line of individuals having the given mutant gene would in most cases have died out, because of the very small detrimental effect which that gene produced on even the heterozygous individuals who carried it. For even an impairment so minute as to cause only a 1 per cent risk of death would, by the force of many such risks, produce one death, on the average, among each hundred individuals having such an unrecognizably small impairment. Hence a gene having such an effect when heterozygous would on the average cause the line of individuals which was transmitting it heterozygously from generation to generation to die out by the hundredth generation. From our knowledge of the frequencies with which given genes arise by mutation it can be reckoned that this number of generations would seldom be great enough to have allowed the given gene to meet its like and become homozygous. The resultant rarity of mutant genes in homozygous condition is a circumstance which reinforces the principle that the great majority of mutant genes carried by an individual produce effects on him which are too small to be recognized individually.

Nevertheless, the individuals of any population do differ from one another very obviously, in numerous ways, and these differences are in large measure caused by the differing mutant genes which they contain. Except for these, they would be as alike as identical twins. Moreover, most of the observed differences are caused by heterozygous mutant genes. This is not really contradictory to our previous conclusion that genes, especially when heterozygous, rarely produce enough effect to be recognized. The fact that reconciles the apparent contradiction is that each individual carries so many heterozygous mutant genes, the great majority of which are different from those of an unrelated individual of the population. So numerous are these genes that they usually do include a few whose individual effects are conspicuous enough to be noted. In addition, many of the genes having effects too small to be noted individually exert by their combined actions effects of considerable magnitude.

Not only are the differences between individuals of the same species mainly caused by the mutant genes which differentiate them, but even the differences between a man and an ape, or a dog, or an oyster, are of this origin. In these cases, however, the individuals are mainly homozygous in regard to the genes differentiating them, and these genes, although to be described as mutant when they arose from their predecessor genes, have been established so long and are so widespread within their species as to have earned the appellation "normal" for themselves in these settings. That is, if the theory of evolution in its modern form is correct, all normal genes were mutant in their day and the whole story of evolution is that of a succession of mutations.

It has, however, been only the very rare mutant gene which survived and became established. Probably not one in a thousand mutant genes proves to be fit in the struggle for existence, since the mutational changes occur blindly, without regard to the end result, and therefore are usually harmful, just as any changes made at random in a complicated working system are much more likely to be harmful than helpful to its working. In fact, so far as civilized man is concerned, we can for our present purposes quite ignore the occurrence of beneficial mutations and simply consider them all as detrimental, so great is the preponderance of the detrimental ones (though it is probably not greater than in many other species), and so little is the likelihood that the rare individual with a beneficial mutation will multiply more than the others. It is this latter circumstance which especially applies to civilized man.

These considerations show the fallacy of the assertion, sometimes made by defenders of the irradiation of human gonads, that the over-all effect of this practice must be the acceleration of the improvement of mankind, by increasing the frequency of beneficial mutations and the consequent speed of evolution. Even without irradiation, enough beneficial mutations must be arising in human populations to *allow* further evolution of a desirable kind to occur, despite the fact that beneficial mutations are so much rarer than detrimental ones. However, evolution *will* occur in desirable directions only when conditions are such as to lead the individuals with the more desirable genes to multiply at a higher than average rate. So far as the conditions influencing the reproduction of modern civilized man are concerned, a good case could be made out for the conclusion that under these peculiar circumstances the individuals with the more desirable mutations do not tend to outbreed the rest and that, in consequence, a desirable type of biological evolution is not to be expected unless deep-seated changes first take place in mores or conditions. In the meantime, it could only be harmful to increase the number of beneficial mutations, inasmuch as, along with each of these, hundreds or thousands of detrimental mutations are simultaneously being engendered.

Some readers following this discussion may be bothered by the feeling that, since the great majority of mutations, although detrimental, produce only minute individual effects on the carrier, they cannot be considered very important. Thus, it might be argued, why may we not ignore them? The answer to this is that we can ignore one, two, or three tiny nuisances, such as grains of dust,

but that when they accumulate greatly, as in the dust bowl, they can become a major curse. It is therefore necessary to consider the method and extent of accumulation of detrimental mutations.

In the past history of man, as of all other species, mutations have occurred and recurred "spontaneously" (that is, without artificial instigation) over the course of countless generations. As a result we all have within us what may be called a load of mutations. Since the vast majority of these are detrimental, even though each one of them usually has a very slight effect, their cumulative action results in a considerable degree of reduction of our "fitness," that is, of our ability to get along. Just how much the fitness is reduced has not been determined. This reduction would be directly observable only by a comparison of existing men with hypothetical, ideally normal men, who of course do not exist and never have existed. Most estimates of the amount of this reduction of fitness, expressed as an increased risk of death before reproduction (or its biological equivalent, failure to reproduce) vary from some 20 per cent to a good deal more. That is to say, under the conditions existing while the human race was evolving to approximately its present biological composition, a hypothetical absolutely normal man would have had a 20 per cent better chance of surviving through the age of reproduction (and of reproducing) than would one having the usual load of mutations.

The question might be raised here, why does the load not increase continually as time goes on, since more mutations must be added to the race in each succeeding generation? The answer lies in the fact that there is a balance or equilibrium reached between the occurrence of mutations in the population and the elimination of these mutations from the population. If it is asked, what eliminates them, the answer is, "natural selection," that is, the lower ability of the individual having more of the detrimental mutations to survive and leave offspring. Natural selection, however, is that cruel process of nature, resulting in death and sterility, which all medical men are trying to help humanity to avoid. That is, they are exerting themselves against natural selection, to save lives. Nevertheless, the more mutations occur, the more elimination must finally ensue, to maintain the equilibrium, although in that case the equilibrium level, or number of mutant genes constituting the average load, would also be raised proportionally. This elimination comes about only through people dying off before the age of reproduction or failing to reproduce. In fact, each detrimental mutation which becomes inherited has eventually, in some generation or other, to effect such an elimination of the line of descent which contains it. It would be inconsistent of a medical man on the one hand to battle natural selection and on the other hand to promote a practice, the induction of mutations, which would result in an increase of natural selection, and an increase in the load of human ills.

The fully lethal mutation that kills unconditionally the first individual in whom it finds expression would at first glance appear to be the worst mutation that can happen. It frustrates a life completely. However, take for comparison with it a slightly detrimental mutation, of the type discussed on page 469, which

reduces the chances of living and reproducing by only 1 per cent. This gives the average individual carrying it only a $\frac{1}{100}$ chance of death before reproduction, or failure to reproduce, as compared with the average individual not carrying it. The carrier would therefore survive and pass along this gene in 99 out of 100 cases, on the average. As previously noted, simple calculation shows that the gene would tend to continue on down through some 100 individuals of later generations, on the average, before it had piled up enough of these $\frac{1}{100}$ risks of dying out to become in fact eliminated, since $100 \times \frac{1}{100} = 1$. In each of these 100 surviving individuals it would on the average have given rise to only $\frac{1}{100}$ as much damage as the fully lethal mutation had caused in the one individual which it damaged. Yet, for the damage as well as for the risk of actual extinction, $100 \times \frac{1}{100} = 1$. Therefore, the gene with so minor an effect does as much damage in the population as a whole, in the end, and gives rise to as much mutational load, as the fully lethal mutation. The same holds true of detrimental mutations of every grade. They differ only in the extent to which they divide up and distribute their load and their risk of death.

To recapitulate this point, mutations which do any damage at all may be regarded as equally harmful to the population and equally obnoxious, regardless of how drastically they affect a single individual inheriting them, since a smaller degree of effect on him is compensated for by the greater number of individuals affected. Hence, to know the total amount of damage done by mutations we have to know, not how large or small their individual effects are and the number of mutations in each category, but only the total number of detrimental mutations produced. This simplifies the problem.

It may next be inquired, how much damage to posterity is caused by a given amount of radiation received by human germ cells? In considering this question, the first point to be recognized is that the frequency of mutations induced by radiation has been found, over a considerable range of doses, to be exactly proportional to the dose received. There is no valid evidence of a threshold dose; that is, all doses, no matter how small, must be considered as carrying some risk, proportional to their size. This is not a controversial matter among geneticists. It is true that some recent work by geneticists in Sweden, Bonnier and Lüning (1949), might be taken as indicating that small doses have effects which are disproportionately large (for their dose size) in producing mutations, but there are other ways of interpreting these results, and at any rate such a principle would be quite contrary to the supposition that there is a threshold below which the effect is lacking.

It has in addition been found that, over an enormous (300,000-fold) range of radiation intensity, it is only the total accumulated dose, not its intensity or duration of application, which counts in determining the frequency of mutations received by the offspring. Moreover, the only radiation having this influence is that absorbed by the gonads themselves, the amount received by other parts of the body being a matter of indifference so far as germinal mutations are concerned. Thus, to calculate the amount of newly induced mutational damage transmitted to an offspring, what one has to know, principally, is the

total dose of radiation received by the germ cells of his two parents over the period of time extending from the conceptions which produced those parents until the conception which produced the offspring in question himself.

At the same time, there are conditions affecting the germ cells in such a way as to make them more or less susceptible to the mutagenic (mutation-producing) influence of any given dose. Chief among these conditions is germ-cell stage: those cells which are at the mature stage of spermatozoon or ovum at the time of irradiation have more mutations induced in them (in Drosophila, about twice as many) as those which are at the immature stage of spermatogonium or oogonium. Hence, to calculate the amount of mutational effect more exactly, one must also know what part of the total dose was received by the germ cells at each of these significantly different stages of the germinal cycle.

It must be admitted that until recently the chief work relating mutation frequency to radiation dose was that conducted on flies, and it is quite obvious that conclusions regarding the absolute quantities of such effects cannot be transferred safely over so great a taxonomic distance as separates flies from men. Nevertheless, I have reported calculations of this kind, as a guide to the results which might be expected if the effects in human beings were quantitatively similar to those in flies, since the data derived from Drosophila were after all more suitable for such use than those derived from fungi or flowering plants.

In view of the great gap between flies and men, it is fortunate that, in recent years, data on an enormous scale have been obtained on mice, by the Russells, working at Oak Ridge (see Russell, 1952). This work is of a precision which matches its magnitude. Contrary to the more usual and easier practice of studying the effects of irradiating spermatozoa, the stage chosen for the study of mutagenesis in this work was that of spermatogonia. These cells afford more representative material for the problem at issue in man than spermatozoa would, since of course the offspring of an irradiated man are in the great majority of cases derived from germ cells which were immature during most of the period of exposure to radiation. There is also reason to infer that the immature germ cells of females have much the same susceptibility as those of males. Moreover, whatever results are obtained from the immature cells are conservative, in that (as previously noted) the frequency of induced mutations is especially low in cells of this stage.

The data, which already in 1950 had involved more than 50 definite, newly induced mutations, reinforced by evidence from controls, have shown clearly that the effect in these mammals is considerably greater than it is in flies. Thus, the use of the results from flies had, quite contrary to the suspicions of opponents, led to a serious *underestimation* of the amount of mutational damage produced by radiation in man, if one may be allowed the reasonable assumption that man more nearly resembles mice than flies in this respect (as he is known to do in practically all other respects). Seven individual genes in mice were chosen in advance for the mutation study, and it was found that, taking the average for these genes, application of 600 r of x-rays to the spermatogonia results in one mutation in any individual gene among about 7,000 gametes

derived from the irradiated spermatogonia. Work by R. M. and J. I. Valencia, J. Kramer, and myself* has shown that it would take about 4,000 r applied to a corresponding stage in flies to induce mutations at this frequency. Thus the mammals appear to be some 6 to 7 times as much affected mutagenically by the radiation as the flies.

It may now be asked, what doses of radiation, applied to this mouse material, would be necessary in order to produce mutations at the same frequency as that with which they arise spontaneously in man? That is, assuming man and mouse to have much the same susceptibility to the mutagenic action of radiation, what dose applied to man would result in an induced mutation frequency equal to the natural (spontaneous) one, and would therefore be followed by a combined mutation frequency (induced plus natural) which was twice the natural one?

A knowledge of the natural frequency per individual gene in man is required for this comparison. Fortunately, there are data on this question, gathered for some half dozen genes, by geneticists specializing on human material (see Haldane, 1949, Neel and Falls, 1951), and these seem to center about the figure of 1 in 50,000. In other words, this figure is indicated as approximately the average for the frequency of spontaneous mutations per gene per generation among human gametes. The actual average may well be considerably lower than this, however, because, first, the genes having an unusually high frequency are *ipso facto* more likely to force themselves on the investigator's attention, and because, second, in some cases similar-appearing mutations of different genes might unwittingly have been attributed to the same gene and thus have resulted in a spuriously high per-gene frequency. One in 50,000 is therefore to be regarded as a maximum figure for spontaneous mutations. Now by using our rule of the proportionality of the induced mutation frequency to the dose of radiation it is readily reckoned from the finding of 1 in 7,000 mutations per gene induced by 600 r that a figure of 1 in 50,000 would be induced by about 85 r. Thus 85 r would result in a doubling of the combined mutation frequency. But if 1 in 50,000 is really much too high a figure for the spontaneous frequency, 85 r would of course result in much more than a doubling.

In mice, 85 r does in fact cause much more than a doubling; that is, the natural mutation frequency is far lower than the frequency induced by 85 r, according to Russell's work. The fact that the spontaneous frequency in mice is much lower than that which we have considered to be representative of man is not at all in contradiction to the idea of a quantitative similarity in the mutagenic reactions of the genes of the two species, however. For the much shorter life of mice and the correspondingly smaller amount of proliferation of their cells give them less opportunity to accumulate spontaneous mutations before they reproduce.

These data have concerned themselves with the mutation frequencies of the individual genes, but these results have somehow to be converted into the collective frequencies for all of the genes in the germ cell before we can estimate

*Work supported by a grant from the American Cancer Society, on recommendation of the Committee on Growth of the National Research Council (see Muller, 1953, [j]).

the total mutational damage caused either spontaneously or by radiation. It is easy to see that, with an average frequency for each gene of one newly arisen spontaneous mutation per generation among 50,000 gametes, a gamete containing a total of 10,000 genes would on the average contain $\frac{1}{50,000} \times 10,000$, or $\frac{1}{5}$, newly arisen spontaneous mutation. That is, there would be one such mutation among every five gametes, in addition to the very numerous "old" mutations (those inherited from earlier generations). And since each individual is derived from two gametes which unite, there would be two "new" mutations among every five individuals. This is a surprisingly high value. However, the number of genes in a human gamete is not known. It can only be judged that it is probably *greater* than 10,000, in view of the fact that evidence derived from several different lines of investigation indicates that even Drosophila gametes contain between 5,000 and 10,000 genes. Some students of the subject consider that human gametes have several times this number, and that the spontaneous mutation frequency in man therefore averages more than one new mutation per person.

These considerations and calculations furnished a part of the basis for the estimate, given earlier in this paper, that the mutational load of man results in at least a 20 per cent risk (and possibly a good deal more) of genetic extinction, and a corresponding loss of fitness, for the average person. In this connection it is to be recalled that the newly arisen mutant genes, like the ones of long standing, seldom affect their carriers recognizably, as individual genes, but that they accumulate over the course of many generations until the load of these numerous tiny moieties is great enough for the resulting disabilities to entail a rate of extinction which just balances the rate at which the mutations are arising. It is unlikely, for the reasons indicated here and elsewhere (see Muller, 1953 [g]), that this rate of genetically caused extinction is less than 20 per cent, or 1 in 5 persons. Thus genetic disability and death, resulting from purely spontaneous mutations, would far exceed those arising from any purely environmental cause.

All that has been said about the effects of spontaneous mutations in man would apply equally to those produced by 85 r of radiation, on the assumption (which must be followed until there is convincing evidence against it) that human and mouse genes react in similar measure to radiation. In fact, even if the per gene *spontaneous* frequency for man has been much overestimated, this would not lead us to lower our estimate for the effect of 85 r or any other dose of radiation, since the mouse data on the amount of radiation effect are solidly based. It would only mean that, *relative* to the spontaneous frequency, the effect of 85 r was correspondingly greater, and that it would involve correspondingly more than a doubling of the natural damage from mutations. At the same time, the damage produced by any other dose of radiation would be proportionate to this.

Our estimates of the spontaneous damage apply to the whole population, since the natural mutations are occurring in everyone in every generation, and they have an opportunity finally to attain an equilibrium with the disability

and elimination which they engender. The amount of damage which has been depicted as arising from 85 r (or a proportionate amount from any other dose) would affect the whole population of any given generation to the extent above calculated only if this was the average amount of radiation received by all the individuals of the population, and if it was received generation after generation for hundreds of years until a new equilibrium of elimination was attained. For radiation received by only a part of the population, the average effect on the whole population is necessarily proportionate to the size of the exposed fraction. And in the case of exposures limited to one or a few generations equilibrium is far from attained. That is, the resulting disability and elimination, although *in toto* proportionate to the radiation received, do not in any one generation become equal to the damage actually done by the radiation, since the damage from any one generation's exposure is spread out very thin, over scores of subsequent generations. While this in no wise lessens it, it makes it virtually impossible to detect.

Granting that the figures here presented are on the conservative side, it remains possible to calculate the minimum amount of mutational damage, or risk of damage, done to posterity by any given amount of radiation received by the gonads of one or more persons who will later reproduce, even though that damage is too elusive ever to be recognized, by reason of its being spread so thin over so many descendants, and at the same time mingled with the damage caused by so many generations of spontaneous mutations. For, despite this elusiveness, the mutant genes are potent enough. Let us then consider how they will affect posterity in some selected case.

Suppose that 255 r of x-rays had been delivered to a woman's ovary for the purpose of inducing ovulation, and that, owing to the "success" of this treatment, she had subsequently fulfilled her desire to produce two children, who rated as normals and who continued her line. Accepting the conclusion that a dose of 85 r results, on the average, in one newly induced mutation among every 5 gametes, the dose of 255 r, being three times this, would result in 3 mutations among 5 gametes. Hence the two eggs which gave rise to the two children of the exposed woman would in the average case contain, between them, $\frac{3}{5} \times 2$, or 1.2 induced mutations. That is, at least one of her two children would usually carry a newly induced mutation.

It is extremely unlikely that this mutation would cause a distinguishable effect or that it would, in this particular generation, result in premature death or a failure to reproduce, but it would nevertheless give this child some slight handicap, which would tend to go on down the generations until it did fulfill its predestined role of acting as an untraceable "straw that broke the camel's back," and, probably in some remote future generation, the line of descent would thereby be cut off. In addition to this final effect, the very slight handicaps experienced by those of intermediate generations would, by reason of the large number of these individuals (a number which tended to be the reciprocal of the degree of damage), add up to the equivalent of a frustrated life, or at least would

play a major part in such an effect. This then would be the price paid by the woman's descendants for her and her doctor's "success" in evading her own feeling of frustration.

Many factors could enter in so as to cut off in some other way the line of descent carrying the mutant gene in question, and thus to prevent (by forestalling it) the occurrence of the denouement depicted. However, it would be equally likely for other factors to cause further multiplication of the line of descent before its final fall, and in this way to multiply the damage. In the long run, such extraneous factors would necessarily balance one another, leaving the above result as the average to be found if a large number of trials were lumped together. It is of course by such averages, which can also be regarded as risks or probabilities, that one's decisions concerning the course of action to be taken in a given case must be guided. In any case involving radiation, then, it is possible to make a provisional estimate of the risk of damage to which all future generations, taken together, would thereby be subjected, and to balance this against the probable amount of benefit to be derived by the present generation. Moreover, in estimating this benefit one must of course take only that amount which is in excess over any probability of benefit which alternative methods of procedure might afford. This then is a kind of ethics which must advance hand in hand with scientific development.

No doubt those not familiar with genetics will experience a feeling of unreality in dealing with these concepts of damage which cannot be demonstrated with a stethoscope, bacteriological culture, or even x-ray photograph, and which leaves its victims apparently hale and hearty. However, the principles of genetics are, in their way, as well established as those of chemistry and physics, and it is no more justifiable to doubt its conclusions regarding the existence and the frequency of mutant genes, just because we cannot directly demonstrate the effects of the individual genes in mixed populations, than to doubt the existence of compounds of given composition, or of atoms and electrons, just because these are so small as to be invisible. For each kind of case, the right kind of controlled setup is necessary for revealing them.

To return by way of conclusion to the flies, it should be observed that the demonstration that x-rays produce mutations and then the more quantitative findings proving their high frequency were possible in this material only by virtue of the very specialized and refined genetic techniques and controlled breeding methods which had been made available in *Drosophila melanogaster,* thanks to nearly two decades of intensive previous work on the part of Drosophila geneticists. If there had been such complete lack of genetic method in the x-ray work with the flies as in the hitherto reported observations on the genetic effect or lack of effect of x-rays on human material, and if fly material had been as heterogeneous, naturally, as human material is, the principle of the mutagenicity of ionizing radiation would never have been demonstrable in flies. In fact, the early experiments on the subject by Morgan, by Loeb and Bancraft, and by others, even though carried out on Drosophila, were entirely inconclusive just because appropriate genetic techniques of sufficient exactitude had not yet

been developed. In these experiments, the parents were irradiated, and numerous offspring of the first and later generations were carefully examined for visible abnormalities, but no consistent differences from the controls, requiring the interpretation that radiation had produced mutations, could be established.

Even today, when very nearly "pure" (homozygous) lines of Drosophila are available for experimentation, if males of this kind are given a high dose of x-rays, such as 3,000 r, and then crossed to equally pure females, it is usually necessary to look through hundreds of first or second-generation descendants before a distinct visible abnormality can be found by these crude means. Yet we know definitely, as a result of much more refined genetic tests, involving studies of the relative fitness or "viability" of groups of later-generation descendants produced by inbreeding, that in actuality each germ cell of the irradiated individuals had had on the average approximately two detrimental mutations produced in it by this dose. The fly population is well able to survive this damage, but only because its high rate of reproduction can compensate for the genetically occasioned extinctions of a high proportion of the lines of descent. That is, an exceptionally drastic "natural" selection has been forced on the population. For, on the average, each newly mutated gene, no matter how small the detriment it occasions, eventually takes its toll in the form of making a major contribution to the extinction of a line of descent. Had we to rely only on direct observations of the visible abnormalities, as seen with ordinary techniques of breeding, we should never have known this.

It is hoped that this discussion will have sufficiently supported the statement, made near the outset of this paper, that the data thus far reported on human beings are irrelevant to the question at issue. It should no longer be possible to doubt the conclusion that detrimental mutations are being produced in highly significant numbers by such doses of radiation as are used for the instigation of ovulation, and that their frequency is indicated by present knowledge to be so high that the over-all harm entailed by such a procedure exceeds its benefit. At the same time, judgments concerning the net benefit accruing from all other uses of ionizing radiation which involve exposure of the gonads require overhauling in the light of modern genetic findings, and the search for methods of reducing the exposure, as well as for methods entirely alternative to irradiation, should be prosecuted actively.

References

Bonnier, G., and Lüning, K. G.: Studies on X-ray Mutations in the White and Forked Loci of Drosophila melanogaster. I. A Statistical Analysis of Mutation Frequencies, Hereditas 35: 183, 1949.

Haldane, J. B. S.: The Rate of Mutation of Human Genes, Proceedings of the Eighth International Genetics Congress, Stockholm, 1948; Hereditas, Supp. p. 267, 1949.

Muller, H. J.:

a. Mutation, in Proceedings of the Second International Congress of Eugenics, New York, 1921: Eugenics, Genetics and the Family, Baltimore, 1923, Williams & Wilkins Company, vol. 1, p. 106.

b. Artificial Transmutation of the Gene, Science 66: 84, 1927.

c. The Effects of Roentgen Rays Upon the Hereditary Material, in Glasser, O., editor: Science of Radiology, Springfield, Ill., 1933, Charles C Thomas, chap. 17, pp. 305-318.

d. Is Radiation a Menace to Posterity? Sci. News Let. 55: 374, 379, 1949.

e. Our Load of Mutations, J. Human Genetics 2: 111, 1950.

f. Radiation Damage to the Genetic Material, in Baitsell, G. A., editor: Science in Progress, New Haven, Conn., 1951, Yale University Press, pp. 93-165 and 481-493.
g. The Manner of Dependence of the Permissible Dose of Radiation on the Amount of Genetic Damage, Acta radiol. (In press.)
h. The Nature of the Genetic Effects Produced by Radiation, in Radiation Biology, New York, McGraw-Hill Book Company, vol. 1, chap. 7. (In press.)
i. The Manner of Production of Mutations by Radiation, in Radiation Biology, New York, McGraw-Hill Book Company, vol. 1, chap. 8. (In press.)
j. A Comparative Study of Mutations Arising Under Different Conditions in Drosophila (Abst.), Eighth Annual Report to the American Cancer Society, 1953, Division of Medical Science, National Research Council, Washington, D. C. (In press.)

Neel, J. V., and Falls, H. F.: The Rate of Mutation of the Gene Responsible for Retinoblastoma in Man, Science 114: 419, 1951.

Russell, W. L.: X-ray Induced Mutations in Mice, Cold Spring Harbor Symposia on Quantitative Biology, vol. 16, p. 327, 1952.

Discussion*

DR. ROBERT RUGH.—As a radiobiologist, a little outside of the clinical field and the straight genetic field, I may say, first of all, the dose to bring about tissue changes in the ovary, in the pituitary, or almost any tissue is thousands of times as great as the dose necessary to bring about a mutational change which can be demonstrated in a subsequent generation. So we are dealing in the ovary or in the testis with extremely sensitive elements histologically or cytologically speaking.

When I went into this field of radiology a few years ago the permissible dose was approximately 1 r per week. The permissible dose was shortly thereafter reduced to .7 r a week for those of us who were working eight hours a day with radiological materials, and now it is .3 r per week. In other words, the more we know about radiations, the more are we respecting radiations, and the probability is that the further restrictions will be in a downward direction.

One of my colleagues at Columbia a good many years ago when they did not know as much about radiation hazards as they do now, a situation which I might compare with our present knowledge of the genetic hazards, inadvertently received exposure to radium which produced in his fingers squamous-cell carcinoma 25 years later. He is currently having that treated with radium, which is ironic. Nevertheless, there is a slow latent histological change brought about by carelessness you might say or rather lack of knowledge at that particular time.

We have now just concluded a long-term experiment in which we gave mice 10 r total body exposure per week for nine months, a total dose of 400 r, which sterilized the females and some of the males. We also treated other mice with 4 microcuries of radioiodine per week which gave them a plateau of constant exposure of 1.76 microcuries per week and some of these females are sterile at 9 months of age. Whether this low dose of iodine, which ablates the thyroids, is directly responsible for the sterilization of these females we are not certain. Nevertheless the sterilization dose is, we believe, far in excess of the dose which would produce genetic changes not necessarily in the first generation but in some future generation. I would like here to amplify, if Dr. Muller will allow me, just one or two points in his discussion because I am certain that some nongeneticists do have an erroneous concept about such matters. From the atomic bomb at Hiroshima they expected that we would now have a generation of monsters as a result of an exposure of the gonads to upwards of 2–, 3–, or 400 r. I don't believe—and Dr. Muller will correct me—any geneticist would expect those who survived and came to birth would show any monstrosities in the first generation at Hiroshima nor would the geneticist expect such monstrosities possibly for many generations. The point which a geneticist emphasizes is that once a mutation is produced, and no more efficient way to produce it is known than by ionizing radiations, it is permanent as long as it is carried from one generation to another generation through the gametes and ultimately if that gene carries a lethal mutation it will express itself. It may be 100 generations hence.

*The opening discussion given by Dr. Ira Kaplan has been omitted, since it forms the basis of an article appearing in the JOURNAL at this time.

Now if the profession is not concerned about what happens 100 or 200 generations hence that is an ethical matter which I suppose should be discussed. I personally am interested in future generations.

One statement was made about radiating the pituitary simultaneously with the ovary to overcome sterility. We have found that animals killed under the x-ray beam given 110,000 r total body exposure show no perceptible histological change in the pituitary gland. Animals given a lethal dose of 1,500 r and dying a week later, having a lapse of time between exposure and death, show no appreciable change in the pituitary gland. A recent paper states that the pituitary gland removed and exposed to 50,000 r shows no depreciation in its follicle-stimulating hormone, so I suppose that the pituitary radiations which have been described in sterility cases may have had no causal relation to coincidental results that have been obtained by simultaneous exposure of the ovaries.

One more point, and that is that the evidence from a mere photograph that a mouse or a child is "normal"—I don't know what that word really means—is totally normal simply because it is alive seems to me to beg the question a bit, inasmuch as we are, I believe, side-stepping the very probable changes that are brought about or being brought about in that child's gonads. Radiation shortens life, increases mutations, etc. It may be many years before we will know the human factor in radiation exposure of the gonads. Nevertheless, there is reason to believe that the same Mendelian mechanisms involved in Drosophila genetics apply in man.

DR. HAROLD JACOX.—My experience parallels Dr. Israel's* almost exactly and the dosage that I have given has been practically the same as his. You will notice that he said 105 tissue roentgens, that is, the tissue dose, and I think it ought to be pointed out that the 85 r that Professor Muller was talking about is an entirely different thing than the 105 r given in the way Dr. Israel says to a particularly localized organ of the body. The total body irradiation, as has been pointed out, is an entirely different thing both biologically and clinically.

The other point that impressed me is the selection of the cases, which I think Dr. Israel has pointed out, and the fact also that we have to balance the good that we may do by this irradiation against the bad that may occur 50 to 100 years from now. I will take the chances on the good.

DR. CARL G. HARTMAN.—I have often quoted the findings of Dr. Murphy of the University of Pennsylvania and now I see that Dr. Israel has followed up that work and agrees with him. Dr. Kaplan has shown that at least in the first generation irradiation of the woman's ovaries does not produce monsters. This was comforting; but Dr. Muller's warning as to remote inheritance of induced harmful recessive characters and the recent experiments with mice (organisms more than half-way from Drosophila to man) worries me.

I would like to ask Dr. Kaplan and Dr. Israel: Why not irradiate the testicles of oligospermic sterile men? Would you expect stimulation there as in ovaries?

I would like to ask Dr. Muller this question: If postpubertal oogenesis from the germinal epithelium should be proved to occur commonly, would you expect radiation to affect also the resting and one might say embryonic undifferentiated epithelial cells of the germinal epithelium, causing gene mutation in them also?

DR. WILLIAM HARRIS.—I have had the opportunity to treat some of these patients and I know that what Dr. Kaplan, Dr. Israel, and Dr. Jacox have said is true, namely, that you can, in a fair percentage of patients, make an infertile woman fertile. I don't think there is any question that the geneticists are correct in stating that ionizing radiation may cause mutations in future generations. I think there is enough evidence, regardless of whether you use Drosophila eggs or bean shoots or mice, that this possibility exists, and it has been shown by geneticists throughout the world. I don't think we can question this fact. This may be a moral issue and may be something that we will not have to consider in our lives

*Dr. Israel's paper appeared independently in this JOURNAL, Vol. 64, p. 971, 1952.

but the generations that follow ours may have to contend with this ugly question. There is one thing I should like to bring up in connection with what the last speaker said. I think that a great deal of risk is encountered by physicians who fluoroscope patients without protection and there is no question but that there must be considerable injury to the testes in the cases of many physicians who do not take precautions to protect themselves.

Life in general is a calculated risk anyhow and you choose only a very small percentage of the population where there is no inbreeding for this treatment. I know that all of you have been confronted with this question where you find a frantic woman who is willing to do anything, even risk her life, so that she can have progeny. In fact, many marriages will depend upon the question of whether or not the woman has a child, and I believe in such a situation if you explain the possibility of mutations in two or three, or 100 generations later, I think that you have covered yourself and done the ethical thing by them.

DR. A. T. WALKER.—There is just one question I would like to ask Dr. Muller. He spoke about spontaneous mutations being so prevalent among human beings. I am just wondering and have often wondered about this, and would like your opinion as to whether or not you think there is any influence of cosmic radiation on these so-called spontaneous mutations. This radiation we get every day, hitting us from here and there, and I wonder whether the bean sprouts and the mice and the Drosophila and *Homo sapiens* also are affected by this cosmic radiation to the extent that spontaneous mutations might result.

DR. LOCKE MACKENZIE.—If one studies these cases of secondary amenorrhea from the point of view of cytology, they seem to fall into two separate categories. The first is the typical secondary amenorrheal picture that Dr. Papanicolaou has described with large numbers of intermediate cells, and more or less cornification. The second group looks exactly like a menopausal picture. It has been our experience that if one stimulates by x-ray the ovaries and the pituitary in the former group one is likely to have rhythmic menstruation follow, while in the second group menstruation does not tend to follow.

I should like to ask Dr. Israel whether or not he has used this criterion as a means of selection of his cases.

DR. INGLIS F. FROST.—There is just one thing I would like to ask Dr. Israel, and that is if he has correlated any of these treatments with endometrial biopsies and with basal temperature charts. I know that patients with irregular periods may have anovulatory periods. I think Dr. Novak puts them about 27 per cent; Dr. Hamblen about 15 per cent. That is about the margin of the anovulatory periods. I have had one patient who has had two periods in her life. She has two children. Another woman had about four periods a year and she has two children. It is possible that if we had given these people x-ray treatment we might have attributed the pregnancies to the x-ray treatment. I think many people have rare ovulatory periods and often we have to find them either by endometrial biopsy or temperature chart. I would like to know if Dr. Israel has correlated these treatments with endometrial biopsies and what they show after x-ray treatment and also the effect on the temperature charts.

DR. WILLIAM H. CARY.—I was familiar with the results of the geneticists in the floral and faunal tests. Therefore, I have never used x-ray for the treatment of sterility except application to the pituitary body, and I must say my results were very disappointing as to stimulating menstruation or the relief of infertility.

I am very much interested in the problem of unilateral oophorectomy. I study the husband and wife as a unit in sterility and we find that some men who have lost one testicle are completely sterile. Another man comes in with one testicle damaged or absent and he is fertile.

I believe that most gynecologists here tonight know of some women who have lost one ovary and seem to have their fertility very little influenced while other women have their

fertility much depressed if not entirely suspended. This suggests to me that in some patients, at least, the two gonads differ greatly in their respective efficiency.

My experience has been that patients who have scant and increasingly scant periods after the loss of one ovary are pretty hopeless patients. I was very interested in hearing Dr. Israel say that he doesn't select these patients for radiation because they do not respond. Is that true?

DR. ISRAEL.—That is correct.

DR. CARY.—Do you notice any relationship between fundal atrophy or hypoplasia and the results you get from radiation?

One should emphasize the importance of self-imposed low diets as a cause of secondary amenorrhea. I can think of five such cases. May we inquire if your patients were studied relative to hypothyroidism?

I understood Dr. Muller to assert that spontaneous mutations were favorable and the artificial ones were unfavorable.

DR. WILLIAM F. FINN.—I wonder if Dr. Israel would tell us whether he has x-rayed only the pituitary or the ovary in patients.

DR. CARY.—And their related importance.

PROF. MULLER (Closing).—You know I maintained there was no controversy.

Among the things that I had meant to mention and didn't was one that came up after I spoke as well as before. Dr. Israel mentioned that one has to distinguish between whole-body irradiation and irradiation of the particular tissue. It happens that that is not true when it comes to the production of mutations. In flies, for example, experiments have been performed, irradiating the whole body or just a portion of the body in which the gonad is present, and you get exactly the same effect when you irradiate that portion of the body as if you irradiate the whole body. It is what the gonad itself gets that counts and that is why the remark here also does not apply. I did not mean 85 r of whole body radiation. I meant 85 r of radiation to the gonad. It happens in the mice the whole body was irradiated for convenience but the irradiation of the rest of the body has nothing to do with the matter so far as the production of mutations is concerned.

As for Dr. Hartman's question, I can answer that radiation would produce mutations in the cells of the germinal epithelium much as in the ova contained in the Graafian follicles.

It was very pleasant to see the pictures of Dr. Kaplan. I could match those with pictures of flies. Taking fly counts of several hundred, I would be able to show all flies perfectly normal so far as we could see in the first generation, in the second generation, or in any generation. It is a mistake to think that mutatious are more likely to show in the second generation than the first. It is in the first generation they are most likely to show as a matter of fact in a mixed-bred population. Moreover, if both parents have been irradiated, say each parent with 40 r, there really isn't any more chance of getting a mutation that will show than if one parent is irradiated with 80 r, if you consider there are also spontaneous mutations in the population, because you are not going to produce the same mutation in the two anyway. As I tried to bring out, it isn't just when the two come together finally through some sort of remote inbreeding that the harmful effect comes into existence.

I am sorry that I gave the impression which Dr. Cary repeated that spontaneous mutations are favorable while radiation mutations are not. Actually, studies show that spontaneous mutations are not more favorable than radiation mutations. They too are subject to this grave objection. We cannot get away from them. We have got to make the best of them. Nature does that by natural selection, which I say we don't like and we are trying to get away from. The reason that evolution has happened in spite of most mutations being unfavorable is because of the cruelty of nature, because there was no medicine and most of the bad mutations therefore died out.

I was asked whether the cosmic radiation that occurs in nature gives an appreciable proportion or frequency of mutations. I calculated the result long ago and recalculated

it recently and I am glad to say that the amount of cosmic radiation, even at very high but attainable altitudes on the earth such as at LaPaz, Bolivia, is not enough to cause significant damage. Of course that word "significant" is an elusive one but the people seem to be all right whose ancestors have lived there for millenia. If you calculate what would happen high up in the aeropause, you can reckon that people, if they lived on an artificial satellite continuously year after year, still would not get as much radiation as the people who were treated for amenorrhea.

Finally, I would concur with the suggestions that have been made that other methods be looked into to accomplish some of these results which radiation has been used for, and I would also say I think it is rather irresponsible, no matter how far postponed the damage, to say, "It is so far in the future that I don't care about it." It is too much like saying, "I shot an arrow into the air. It fell to earth I know not where, and therefore I do not care."

THIRD GENERATION FOLLOW-UP OF WOMEN TREATED BY X-RAY THERAPY FOR MENSTRUAL DYSFUNCTION AND STERILITY TWENTY-EIGHT YEARS AGO, WITH DETAILED HISTORIES OF THE GRANDCHILDREN BORN TO THESE WOMEN

IRA I. KAPLAN, B.S., M.D., F.A.C.R., NEW YORK, N. Y.

WHEN in 1925, I first began to apply low-dosage x-ray therapy for the treatment of female sterility, I was interested in noting the effect on the children born of women so treated. In 1928,[1] I reported the results of irradiation in 30 cases treated over the course of the previous seven years, with the observation that all of the 7 children born to these treated women were normal in every respect and exhibited no determinable genetic injury. I also realized that whether or not these children had acquired any genetic injury from irradiation which might be transmitted to a future generation would have to be observed in the progeny of these children following their marriage. This required a waiting period of at least 20 years, and such a waiting time was exacted of me before I was able to report on the grandchildren (third generation) of the originally irradiated infertile women treated over 20 years ago.

It was not until Muller,[2] in 1950, had made his announcement that dire consequences to later generations would result from genetic injuries due to irradiation that observations of grandchildren of irradiated infertile women assumed importance.

In order to report properly on the observations of grandchildren of irradiated infertile women, a review of the problem of radiation therapy in such cases, and a report of the results accomplished over a period of 28 years is definitely worth while.

During the period from October, 1924, until October, 1953, there were referred to me in private practice 660 married women for x-ray treatment for the relief of sterility. The diagnosis in all these cases was made by the referring gynecologist, and irradiation was advised only when all other procedures had been tried and proved unavailing.

Of the 660 patients treated by me, I was successful in tracing all but 219 for one or more years after therapy was administered. Of the 441 whose records are known, 270 are definitely known to have become pregnant following treatment with x-ray therapy, administered to the ovaries and pituitary. These women have given birth to 347 apparently normal children. There were five cases of ectopic pregnancy. Twenty-seven women who had failed to respond to therapy and who adopted children did not subsequently succeed in conceiving. In two cases hysterectomy followed treatment; later examination in two nonresponsive cases revealed completely closed tubes; two women whose amenorrhea was relieved did not conceive because the husbands on re-examination were

found to be definitely impotent; and one woman died of leukemia a year following irradiation. In 104 cases definite failure was reported. Twenty-eight patients were too recently treated to respond with pregnancy.

When, in 1924, irradiation as a therapeutic measure for treatment of female sterility was suggested to me by Dr. I. C. Rubin, like many others I believed at that time that, because large doses of x-ray produced sterilization in the female, perhaps a minimal dose of x-ray applied to the ovaries would in some manner act as a stimulant to ovarian activity and relieve the condition of sterility. Today this idea of stimulation is no longer tenable. Although, in 1905, Halberstädter[3] proved that x-rays have a specific affinity for the ovaries, in what way the functional reaction occurs was not defined. Today we no longer believe irradiation is a direct stimulative process but, no matter what the cause of the favorable response, and while I cannot offer a definite explanation as to why the x-ray produces favorable results as it does in many cases, the clinical demonstrations recorded by me, I believe, as do Israel[4] and others, prove without doubt that low dosage x-ray therapy does successfully relieve menstrual dysfunction and sterility.

The age of the women treated varied—the youngest was 18 and the oldest 40 years old. The most favorable results were achieved in the 20 to 35 year group.

At first x-ray to the ovaries alone was tried. When however, it was noted that only a few cases responded to irradiation directed only to the ovaries and based upon the observation of Béclère[5] and others that irradiation to the pituitary was instrumental in restoring the menstrual function in some women so treated, I sought to improve results by treating all cases with the x-ray administered to both the ovaries and the pituitary. This procedure proved especially effective in those cases exhibiting hirsutism, overweight, clinical pituitary imbalance, or pituitary adenoma.*

In several cases the referring physician requested irradiation to the pituitary alone. Only two cases in my series responded successfully to irradiation administered only to the pituitary.

In such cases, where the patient fails to conceive a second time following a previous successful pregnancy, or where she fails to conceive following a previous miscarriage, and irradiation is administered with a resultant successful subsequent pregnancy, I believe that the result is achieved through the effect of the x-ray on a persistent corpus luteum. The records of a number of such cases appear to bear out this assumption.

In 1935, Stein and Leventhal[6] called attention to amenorrhea and sterility associated with polycystic ovaries and suggested destruction of the cysts for relief of sterility. In a number of cases received for irradiation where ovarian cysts were associated with the sterility, irradiation seemingly acting in a manner similar to surgery, relieved the sterility, and the patients conceived. There are a number of such cases in my series. In some cases cystic conditions were surgically proved.

*Due to space limitations the detailed histories of these and subsequent case reports could not be cited in this paper.

While in many cases there appears to be a specific reason for the sterility, as already enunciated, in the majority of cases referred for irradiation the dysfunction is apparently due to a general imbalance within the mechanism associated with menstruation, ovulation, and conception. Relief was achieved with irradiation in an appreciable number of such cases in my series.

In some cases, although sterility was relieved by x-ray therapy, the patient miscarried shortly after conception. Kleegman,[7] Wolf,[8] and others suggest that this mishap occurs because conception took place too soon after the irradiation. The incidence of miscarriage in my series after irradiation is, however, no higher than that occurring in the normal-pregnancy group. That immediate pregnancy following irradiation does not, however, always presage miscarriage has been noted in a number of cases treated by me.

In several instances where the patient conceived and miscarried after irradiation, she conceived a second time without difficulty and successfully bore children, in many cases bearing several normal children.

The length of time sterility has existed apparently affects the response to irradiation; the shorter the period, the better the response. In my series the period of sterility existed for a few months and in some cases for 17 years before irradiation was administered. A large number of women sterile for 5 years or more responded well to irradiation.

The following case of sterility for 13 years is worth description.

Mrs. E. R., aged 33 years, was referred for treatment of irregular menstruation and sterility on Jan. 24, 1944. The menarche appeared at 13 and periods were always irregular in spite of treatment. She married at the age of 20, had been treated for many years without effect, and remained sterile for a period of 13 years. X-ray therapy was then advised and administered to the pituitary and ovaries on Jan. 24, 31, and Feb. 7, 1944. She responded well, menstruated normally for three months, conceived, and on April 5, 1945, gave birth to a normal baby boy. She continued to menstruate normally but willfully prevented pregnancy until 1952. She then again readily conceived and on Nov. 13, 1952, gave birth to a normal baby girl.

Irradiation, in my experience, employed for the treatment of amenorrhea in unmarried girls, is not harmful and after restoration of normal periods they may marry and bear normal children. I have an appreciable number of cases in this category.

It often happens that at puberty a young woman may have excessive bleeding associated with the establishment of her menstruation. In some cases this excessive bleeding may be controlled by hormone therapy. However, when such procedures fail, surgery rather than irradiation may be suggested because of the erroneous supposition that irradiation when used in young, unmarried women will, if employed for the control of puberal bleeding, be likely to precipitate permanent amenorrhea and subsequent sterility. In my experience, when irradiation was judiciously applied, in many cases to the spleen alone or to the pituitary, bleeding was effectively controlled without inhibiting the woman's subsequent ability to conceive. The following case illustrates such effects:

Mrs. F. C. was first referred for x-ray treatment at the age of 14½ years, on Nov. 17, 1931, for severe depleting puberal hemorrhage, after all other medication failed. During the course of 6 years, she received several courses of pelvic x-ray and occasional pituitary treatment. She responded well and the condition apparently was permanently controlled in 1937. In September, 1939, at the age of 22, she married, functioned normally, conceived without difficulty and bore four normal children, a girl on Feb. 10, 1942, a boy on April 12, 1945, a girl on Oct. 16, 1946, and a girl on April 18, 1950.

Now as for the question of genetic effects on human progeny of irradiated women. The genetic dangers, derived from the results of animal experiments, such as Muller's,[9] cannot properly be applied to the problem in human beings. The basis of all these adverse pronouncements is Muller's observations on the effects of irradiation on the Drosophila flies. After a personal experience of 29 years with x-ray therapy, I believe with Haldane[10] and Glücksmann[11] that one cannot properly nor justifiably extrapolate genetic injuries noted in experimentally irradiated animals to human beings therapeutically treated for sterility with low-dosage x-ray. No one has been able to demonstrate the occurrence of genetic abnormalities in the progeny of properly therapeutically irradiated women definitely comparable with the genetic injuries noted in experimental animals following irradiation. In evaluating the genetic injuries from the x-rays, the geneticist states that lethal injuries disappear immediately. Dormant mutations, if lethal, become evident only when they are present in sufficient numbers to provide a chance of their coming together in the mating of two individuals carrying them. The Atomic Bomb Casualty Commission recently reported that in Hiroshima and Nagasaki no adverse genetic effects were noted in the progeny of women who survived irradiation from the atomic bomb explosion, even though the "r" irradiation received by these women was very much greater than the therapeutic x-ray.

In a population of 180 millions, the chance that progeny of an irradiated mother will marry progeny of another similarly irradiated mother is rather remote. There are probably no more than two to three thousand women in the United States at present who have borne children following irradiation. Therefore, the chance of genetic injury, as the result of the mating of individuals with genes defective from radiation is small indeed. In animal investigation, generations may be produced in the matter of days or months, whereas, in the study of irradiation effects in human beings, at least 20 years must elapse before one can reproduce even a third generation.

This long waiting period has been required of me and it was only when the first baby born of an irradiated mother grew up, matured, and married at the age of 20 that I was able to see the first of the third generation group, that is, a grandchild of an originally irradiated sterile woman. This first married daughter of an irradiated sterile mother has already given birth to a second normal child. The father of this boy and girl of the third generation, himself a pediatrician, has satisfactorily determined that both these children are mentally and physically normal in every respect.

At the present time I am able to record the marriage of 20 children of 15 women originally treated with x-ray therapy for sterility over 25 years ago.

These 20 married children have already produced 14 grandchildren, that is, third-generation grandchildren. In one case twin grandchildren have been born to the second daughter of an originally irradiated mother. At present 3 more married children are pregnant and expected to be delivered shortly.

All these grandchildren are mentally and physically normal. What these grandchildren will produce after their subsequent marriage must await an observation period of another 20 years.

My interpretation of the results of irradiation in the treatment of sterile women is based entirely on clinical follow-up observations, which include mental and physical examinations, and on the actual evidence of successful functional responses and ability to produce offspring. I believe the 347 living children and already existing 14 grandchildren born of irradiated grandmothers to be ample proof of the propriety of using x-ray therapy for female sterility. The 14 living normal grandchildren of the originally irradiated women already recorded further demonstrate the physical and normal development of such progeny without any demonstrable abnormalities noted by competent pediatricians.

These clinical examples of normal results from irradiation apparently support the belief that the adverse results experienced in animal investigations may not be properly applied to human experience and that therapeutic low-dosage irradiation is a proper procedure in the treatment of female sterility.

The following case histories illustrate the facts regarding the birth of these third generation grandchildren.

Mrs. C. A., aged 28 years, was referred in June, 1925, for sterility. She had married at the age of 26. Following x-ray to the ovaries she conceived and gave birth to a baby girl on Dec. 21, 1926. This girl married in March, 1946, conceived and gave birth to a baby boy on Oct. 25, 1948, and a baby girl on Oct. 13, 1950. These two grandchildren of Mrs. C. A. are normal in every way.

Mrs. H. B., aged 22 years, was referred in March, 1925, for sterility. She married at the age of 21. Following x-ray to the pituitary and ovaries she gave birth to a baby girl in January, 1926. This girl married in March, 1949, conceived, and gave birth to a baby boy on Aug. 30, 1950, a perfectly normal grandchild of Mrs. H. B. The daughter is at present again pregnant and is due to give birth to a second child in November, 1953.*

Mrs. M. M., aged 24 years was referred for sterility on Feb. 22, 1927. She married at age 21. She received x-ray therapy and conceived, and on Nov. 18, 1928, gave birth to a baby boy; on Aug. 29, 1930, to a baby girl; on Aug. 8, 1934, to a baby girl; and on July 18, 1940, to another baby girl. After serving in the armed forces the boy married in 1949, and on March 10, 1950, his wife gave birth to a normal baby boy, and on Oct. 26, 1951, to a baby girl, normal grandchildren of Mrs. M. M.

The eldest daughter of Mrs. M. M., born in August, 1930, married in January, 1952, at the age of 22, conceived, and on Aug. 20, 1952, gave birth to twins, a boy and a girl, normal grandchildren of Mrs. M. M.

On Sept. 28, 1952, the second daughter of Mrs. M. M., born in August, 1934, was married in the spring of 1952, at the age of 18, but as of April, 1953, has not yet conceived.

Mrs. L. K., aged 31 years, was referred in March, 1926, for sterility. She married at the age of 29. Following x-ray therapy she conceived, and on March 20, 1927, gave birth to

*Normal baby boy, born Nov. 7, 1953.

a baby boy, and on June 28, 1929, to another baby boy. In October, 1932, she had a therapeutic abortion. Her first boy married in 1950 and on Sept. 24, 1951, his wife gave birth to a baby boy. The second son is in the Army and, as of 1953, has not yet married.

Mrs. L. S., aged 33 years, was referred in January, 1925, for sterility of 15 years' duration. She was married at the age of 17. Following x-ray treatment she conceived, and on March 19, 1926, gave birth to baby boy; on March 7, 1929, to a baby girl; and on April 13, 1930, to a baby boy. In February, 1931, a miscarriage occurred. Her second child, the daughter, married on Nov. 19, 1949, conceived, and on March 29, 1951, gave birth to a baby girl, and on Feb. 11, 1952, to a baby boy, both normal grandchildren of Mrs. L. S.

The oldest son of Mrs. L. S. was married on Oct. 29, 1951, but as yet his wife has purposely not conceived.

Mrs. M. Me., aged 25 years, was referred for sterility on Feb. 21, 1927. She married at the age of 21. Following x-ray therapy she conceived and on January 31 gave birth to a baby girl. This girl married in November, 1951, and, on Sept. 6, 1952, gave birth to a baby boy, a normal grandson of Mrs. M. Me.

Mrs. E. R., aged 22 years, was referred on Oct. 10, 1928, for sterility. She married at the age of 19. Following x-ray therapy she conceived and on Aug. 30, 1929, gave birth to a baby girl; on Aug. 2, 1931, to a baby boy; and on Feb. 4, 1936, to a baby girl. The oldest daughter of Mrs. E. R. was married on Sept. 23, 1951, conceived, and on Sept. 23, 1952, gave birth to a baby boy, a normal grandson of Mrs. E. R.

Mrs. F. C., aged 30 years, was referred on Oct. 14, 1927, for scanty menstruation and sterility. She was a large, very obese woman. She married at the age of 22, became pregnant late in 1925 and in August, 1926, was delivered of a full-term, stillborn baby. Subsequent menstruation was scanty, lasting scarcely a day. She was then referred for x-ray therapy. She responded well, conceived in 1930, and on march 18, 1931, was delivered of a normal baby boy by cesarean section. In 1933 she died of intercurrent disease. The son, born in 1931, developed normally, enlisted in the Marines, and then was married on Jan. 6, 1951. His wife became pregnant and gave birth to a baby boy on March 1, 1953, a grandson of Mrs. F. C.

Mrs. M. B., aged 24 years, was referred on Oct. 10, 1927, for sterility. She married at the age of 21. Following x-ray therapy she conceived and on Aug. 18, 1928, gave birth to a normal baby girl. She conceived again twice but miscarried both times. The daughter, born in August, 1928, matured, functioned normally, and married a young naval officer on Nov. 22, 1950. On Oct. 16, 1953, she gave birth to a normal baby girl, granddaughter of Mrs. M. B.

Mrs. M. U., aged 28 years, was referred on Aug. 12, 1927, for sterility. She married at the age of 20. Following x-ray therapy she conceived and on Aug. 24, 1928, gave birth to a baby girl. This girl was married on Nov. 22, 1952. She is now pregnant.

Mrs. S. E., aged 24 years, was referred for sterility on Oct. 22, 1924. She married at the age of 21. Following x-ray therapy she gave birth to a baby boy on Oct. 15, 1925, and another boy on April 25, 1927. The older boy, now a young physician still serving his hospital residency, married on Nov. 9, 1952. His wife is now in the fifth month of pregnancy.

Mrs. J. L., aged 22 years, was referred in April, 1935, for irregular menstruation and sterility. She had married at the age of 20. She was a short, obese, hairy woman. Following x-ray therapy she conceived and on March 30, 1936, gave birth to a baby girl; on June 16, 1938, to another girl; on Oct. 29, 1942, another girl; and on July 31, 1947, a boy. The girl born on March, 30, 1936, married on April 26, 1953, and is now expecting a child, a grandchild of Mrs. J. L.

I have been able to trace a number of women treated by me for sterility more than 20 years ago whose child or children born following irradiation have married but as yet have produced no grandchildren.

Mrs. I. G., aged 30 years, was referred for irregular menstruation and sterility of 2 years' duration following a previous miscarriage. She married at the age of 23. Following x-ray treatment she conceived and on Nov. 10, 1927, gave birth to twin girls and on Sept. 14, 1930, to a boy. On Oct. 27, 1951, one of the twin girls married but has as yet not desired a child. The son, in the Armed Service, married in March, 1951, and his wife became pregnant, but shortly following this event they were divorced and she had an abortion.

Mrs. M. R., aged 28 years, was referred on July 31, 1930, for sterility of 6 years' duration. She married at the age of 22 years. Following x-ray therapy she conceived, and on July 17, 1931, gave birth to a normal boy. She continued to function normally and on Nov. 28, 1934, gave birth to a second boy. The first boy, born in 1931, married in December, 1952, and has moved to California. I have not yet been notified about any offspring.

Mrs. B. C., aged 26 years, was referred on Oct. 27, 1927, for sterility of 5 years' duration. She married at the age of 21. Following irradiation she conceived and bore a son on Nov. 27, 1928. This boy was married on Oct. 16, 1953, too short a time as yet to produce offspring.

Conclusion

This study is based upon the results noted in 660 infertile women treated with high-voltage or low-dosage x-ray therapy over the past 28 years. I have been able to trace 270 such married women who successfully became pregnant following such treatment and I have a record of 347 normal children subsequently born to them. These children are normal in every respect.

I have been able to trace 34 of these children whose mothers were treated 20 or more years ago. Twenty of them have already married and up to the present time have produced 14 normal living children, that is, third-generation children or grandchildren of the women originally treated with x-ray therapy for sterility. Three of these married children are at present pregnant and, therefore, three more grandchildren can be expected shortly.

All of these grandchildren have been proved to be normal in every respect.

The results, therefore, indicate that irradiation, when properly used, is harmless to the treated woman and to her progeny's offspring, and no adverse genetic effects are noticeable in either the second or third generation of such irradiated women.

References

1. Kaplan, I. I.: Am. J. Obst. & Gynec. **15**: 658, 1928.
2. Muller, H. J.: Am. Scientist **38**: 33, 1950.
3. Halberstädter, L.: Berlin klin. Wchnschr. **42**: 64, 1905.
4. Israel, S. L.: Am. J. Obst. & Gynec. **64**: 971, 1952.
5. Béclère, A.: Arch. Roentg. Ray. **14**: 142, 1909-1910. (Abst.)
6. Stein, I. F., and Leventhal, M. L.: Am. J. Obst. & Gynec. **28**: 181, 1935.
7. Kleegman, S.: Personal communication.
8. Wolf, S.: Am. J. Obst. & Gynec. **59**: 259, 1950.
9. Muller, H. J.: Science **66**: 84, 1927.
10. Haldane, J. B. S.: Brit. J. Radiol. (supp. 1), p. 99, 1947.
11. Glücksmann, A. M.: Brit. J. Radiol. (supp. 1), p. 101, 1947.

755 Park Avenue
New York City

THE VANDERBILT COOPERATIVE STUDY OF MATERNAL AND INFANT NUTRITION*

V. Description and Outcome of Obstetric Sample

WILLIAM J. MCGANITY, M.D., RICHARD O. CANNON, M.D., EDWIN B. BRIDGFORTH, A.B., MARGARET P. MARTIN, PH.D., PAUL M. DENSEN, SC.D.,** JOSEPHINE A. NEWBILL, B.S., G. SYDNEY MCCLELLAN, M.D., AMOS CHRISTIE, M.D., J. CYRIL PETERSON, M.D.,*** AND WILLIAM J. DARBY, M.D., PH.D.,
NASHVILLE, TENN.

(From the Division of Nutrition of the Departments of Biochemistry and Medicine, the Departments of Preventive Medicine, Obstetrics and Gynecology, and Pediatrics and the Tennessee-Vanderbilt Nutrition Project, Vanderbilt University School of Medicine)

NUMEROUS reports have dealt with the relationship of nutrition to the prenatal course and the maternal and fetal outcome of pregnancy. The conclusions have been conflicting. Ebbs, Tisdall, and Scott[1] and Burke and associates[2] found a significant relationship between the mother's diet during pregnancy, and the incidence of maternal complications and fetal abnormalities. In contrast, Williams and Fralin[3] and Smith[4] were unable to demonstrate such striking correlations between the nutrient intake of the mother and the course of pregnancy and/or the maternal and fetal outcome. Most of such studies were made on series of patients who were selected from a much larger group of available patients, with nutritional evaluations based upon dietary history alone. The results may reflect an accurate assessment of the groups studied but do not necessarily represent the true situation of the whole groups that were available for study. In addition, the classification by estimated dietary intake alone has failed to define adequately the level of nutrition of the selected subjects.

Early in 1945, six groups in the Vanderbilt University School of Medicine found their interests had converged on the study of the effects of nutrition on the maternal and fetal outcome of pregnancy. They joined in a study designed to assess the nutriture of all the pregnant women who received their prenatal care and delivery at the Vanderbilt University Hospital, and to allow the investigation of any relationship which existed between the nutriture of these patients and the course of pregnancy, labor, puerperium, and the condition of the infant.[5] Every patient who was admitted to the prenatal clinic during the four years of the study (September, 1945, through February, 1949) was entered in the group. The only selection factor was the "natural" selec-

*Financial assistance which has made possible this program has been generously provided by grants from the following organizations: the Nutrition Foundation, Inc., the International Health Division of The Rockefeller Foundation, the United States Public Health Service (RG-278 through RG-A-4[C6]), the Tennessee Department of Public Health, and Distillation Products, Inc.

**Present address: Department of Biostatistics, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, Pa.

***Present address: Department of Pediatrics, Marquette University, Milwaukee, Wis.

tion that brought the patient to Vanderbilt University Hospital rather than to other available clinics in our area. The data, therefore, define the level of nutriture of all our clinic patients.

During the four-year period 2,338 white patients were entered in the study. The economic status of these women fell in the low to moderate income range. Eligibility for both prenatal and hospital care (within the restrictions of minimum and maximum gross income of $1,200 to $3,000 per annum) was determined by the hospital social service on the basis of needs, debts, and dependency. When the study was initiated in 1945, some patients were admitted for out- or inpatient care without charge; others were charged at minimal rates. In 1947 the pay system was altered so that all patients were charged minimal fees.* The patients were hospitalized for delivery on the wards of the obstetric service of Vanderbilt University Hospital.

From the sample of 2,338 patients, 292 have been excluded from this report because of incomplete obstetric records or other causes. This excluded group has been statistically considered in a previous paper (Darby and coworkers[5]) and the conclusion reached that their attributes were similar to the pattern of the main group of patients.

This report, then, deals with the obstetric and immediate infant outcomes of 2,046 deliveries which occurred at the Vanderbilt University Hospital between 1945 and 1950. These are believed to describe adequately the experience of those patients receiving care in our clinic. The second portion of this report will deal with the interpretation and correlation of these results with physical, dietary, and biochemical data. A detailed outline of methods and procedures is to be found in another publication.[5] It will suffice for the present to say that once during each trimester, and at the six weeks post partum check, a nutritional evaluation of each patient was made by physical examination for clinically detectable evidence of deficiencies, biochemical assessment of body fluids for protein, vitamins, and others, and nutritional dietary records for seven-day periods. We propose to define the nutritional level of our patients, to evaluate methodology of nutritional study, and to study the question for our group of patients, "What were the relationships of nutrition to the obstetric and infant outcomes?" In order to interpret the generality of the applicability of the conclusions, a detailed description of the composition of the group is essential.

Of the 2,046 patients who had complete obstetric records, approximately one-third (32.2 per cent) were primigravidas. All of the patients were white; 1,953 were married, 52 were single, and 41 were widowed or divorced.

The age-parity relationship of the group is shown in Tables I and II. There were 79 per cent under 30 years of age, with 55 per cent between 20 and 30 years. There was the expected high concentration of patients having their first baby before 20 years of age, with a correspondingly large propor-

*Fees per visit to the outpatient clinic ranged from 25 cents in 1945 to $1 in 1949, and minimal charges for hospitalization for delivery ranged from $21 to $60 during this interval.

TABLE I. PERCENTAGE DISTRIBUTION OF PATIENTS ACCORDING TO AGE WITHIN PARITY GROUPS
TOTAL NUMBER = 2,046

		AGE IN YEARS ON DISCHARGE					TOTAL
		< 20	20-24	25-29	30-34	≥ 35	
	NUMBER	496	706	415	224	205	2,046
ALL PARITIES COMBINED	%	24.3%	34.5%	20.2%	11.0%	10.0%	100%
Para 0		56.2%	33.0%	6.7%	2.7%	1.4%	100%
Para i-ii		15.8%	49.6%	24.8%	6.0%	3.9%	100%
Para iii-iv		0	27.8%	36.6%	23.7%	11.9%	100%
Para v+		0	3.4%	21.9%	30.1%	44.5%	100%

TABLE II. PERCENTAGE DISTRIBUTION OF PATIENTS ACCORDING TO PARITY WITHIN AGE GROUPS
TOTAL NUMBER = 2,046

		PARITY				TOTAL
		0	i-ii	iii-iv	v+	
	NUMBER	658	801	295	292	2,046
ALL AGES COMBINED	%	32.2%	39.2%	14.4%	14.3%	100%
< 20 years		74.6%	25.4%	0	0	100%
20-24 years		30.7%	56.2%	11.6%	1.4%	100%
25-29 years		10.6%	47.8%	26.1%	15.5%	100%
30-34 years		8.0%	21.4%	31.2%	39.3%	100%
≥ 35 years		4.4%	15.1%	17.1%	63.4%	100%

TABLE III. DISEASES ASSOCIATED WITH PREGNANCY
TOTAL = 225
(Total Conditions in 2,046 Women)

Infectious or Parasitic.—	
Active and quiescent tuberculosis	23
Fibrosis of lung, post-tuberculosis	12
Syphilis, initial infection, treated during pregnancy	8
Syphilis, old infection	58
Gonococcal infections	10
Measles	2
Whooping cough	1
Mumps	1
Malaria	2
Endocrine Disorders.—	
Diabetes mellitus	7
Diabetes insipidus	1
Hypothyroidism	3
Diffuse, nontoxic goiter	13
Disease of pituitary gland	1
Disease of Circulatory System.—	
Rheumatic heart disease	11
Hypertensive cardiovascular disease	10
Phlebitis, thrombophlebitis (ante partum)	2
Disease of Genitourinary System.—	
Pyelitis, cystitis, pyelonephritis (ante partum)	44
Orthostatic albuminuria	1
Disease of Nervous System.—	
Epilepsy, grand or petit mal	7
Other Abnormalities.—	
Bony pelvic abnormalities	
Due to malformation	4
Due to rickets	1
Due to tuberculosis or streptococcus	3

tion of multiparous patients over the age of 30. The incidence of primigravidity among patients over the age of 35 years was 4.4 per cent.

Table III lists those conditions that were associated with pregnancy, which pre-existed or occurred during this pregnancy, but were not peculiarly a result of pregnancy. There were 225 (11.0 per cent) conditions which might have some bearing on the ultimate fetal or maternal outcome. These included 35 cases of tuberculosis in various stages of the disease; 76 patients with venereal disease (gonorrhea and syphilis), 8 of which had the initial infection and treatment during the present pregnancy; 7 cases of diabetes mellitus; 21 cases of rheumatic or hypertensive cardiovascular disease; 7 cases of epilepsy, either grand or petit mal in type; and 8 patients with bony abnormalities of the pelvis.

A list of conditions peculiar to or complicating pregnancy is given in Table IV. Pre-eclampsia* or eclampsia† occurred in 5.0 per cent of the patients. Our 4.5 per cent incidence of pre-eclampsia may be compared with the incidence of this condition as reported in the studies of Ebbs, Tisdall, and Scott[1] with 4.8 to 5.7 per cent, Burke and associates[2] with 13 per cent, and Tompkins and Wiehl[6] with 4.1 per cent for their control groups (see Table XII). The pre-eclampsia rate for primigravidas was twice that for multigravidas. The largest number of cases of pre-eclampsia was in primigravidas under 20 years of age, but the *rate* of occurrence increased with age. In the primigravidas under 25 years of age the incidence was 5.5 per cent, whereas over 25 years it was 14.1 per cent. Similarly, in the multigravidas under 25 years the incidence of pre-eclampsia was 2.3 per cent, and over 25 years it was 4.0 per cent.

TABLE IV. INCIDENCE* OF CONDITIONS PECULIAR TO PREGNANCY IN 2,046 PATIENTS

	ALL PATIENTS	PRIMIGRAVIDAS	MULTIGRAVIDAS
1. Hyperemesis gravidarum	15 (0.7%)	6 (0.9%)	9 (0.6%)
2. Pre-eclampsia	93 (4.5%)	48 (7.1%)	45 (3.3%)
3. Eclampsia	10 (0.5%)	8 (1.2%)	2 (0.1%)
4. Polyhydramnios	13 (0.6%)	1 (0.2%)	12 (0.9%)
5. Placenta previa	7 (0.4%)	2 (0.3%)	5 (0.4%)
6. Premature separation of placenta	24 (1.2%)	8 (1.2%)	16 (1.1%)
7. Anemia (Hgb. < 10 Gm./100 ml.)	232 (11.3%)	68 (10.3%)	164 (11.8%)
8. Rh-negative blood (for comparison)	334 (16.3%)	107 (16.3%)	227 (16.4%)
Total number of patients	2,046	658	1,388

*The number in parentheses is the percentage of the total of each class of patients exhibiting the condition.

Vaginal bleeding during the third trimester occurred in 1.5 per cent (31) of our cases; placenta previa in but 7 patients—5 multigravidas and 2 primigravidas; and premature separation of a normally implanted placenta occurred in 24 cases—16 multigravidas and 8 primigravidas. The *incidence,* on the other hand, of placenta previa was 0.4 per cent for multigravidas and 0.3

*Pre-eclampsia: the development, after the twenty-fourth week of pregnancy, of sustained hypertension and significant proteinuria, and/or edema in a previously normal gravid woman. Although it is most commonly a disease of the last trimester it may rarely occur prior to the twenty-fourth week.

†Eclampsia: the occurrence of convulsions and/or coma in a pregnant or puerperal woman superimposed on the signs of pre-eclampsia.

per cent for primigravidas. Similarly with premature separation of the placenta, the *incidences* were 1.1 per cent and 1.2 per cent, respectively. There were 232 (11.3 per cent) patients with a hemoglobin level less than 10 Gm./100 ml. of whole blood during one or more trimesters or during the postpartum period. This 11 per cent incidence may be compared with that reported by Ebbs, Tisdall, and Scott[1] of 22 per cent, Bethell, Blecha, and Van Sant[7] of 25 per cent, and Burke and collaborators[2] of 5 per cent (see Table XII). Of these 232 patients, only 37 had microcytosis and hypochromia, and one patient had a macrocytic anemia. These findings will be discussed in greater detail in the second part of this report.

The 2,046 pregnancies resulted in 2,068 infants and fetuses, including 22 sets of twins (Table V). Mature infants (who weighed 2,500 grams or more) numbered 1,909 (92.3 per cent). There were 139 (6.7 per cent) premature or immature infants, who weighed from 400 to 2,499 grams. This incidence of prematurity may be compared with that calculated from the data of other studies: 7.5 per cent, Tompkins and Wiehl[6]; 4.2 per cent, Burke and associates[2]; and 5.2 per cent, Smith[4] (see Table XII).

TABLE V. OUTCOME OF PREGNANCY IN 2,046 PATIENTS

	MATURE	PREMATURE	ABORTIONS
2,024 single pregnancies	1,888	116	20
22 twin pregnancies	21	23	0
2,046 pregnancies = 2,068 infants	1,909 (92.3%)	139 (6.7%)	20 (1%)

The apparent incidence of abortions in our series was very low (1.0 per cent). This is due, in part, to the restriction of our considerations to patients who were delivered in the hospital. It is recognized that most abortions occurred in unhospitalized patients. In the excluded cases, there were an additional 20 abortions. If these be included the total becomes 40 abortions in 2,129 pregnancies (1.9 per cent) which corrects to 40 abortions in 919 (4.4 per cent) patients who were entered in the study prior to the twentieth week of gestation. (Abortion is defined as delivery of a fetus of less than 400 grams in weight prior to the twentieth week of gestation.) We realize that none of these figures (1.0 per cent, 1.9 per cent, 4.4 per cent) approximates the commonly accepted estimates. A probable explanation is that many early abortions do not reach the prenatal clinic.

The calculated periods of gestation were less than 38 weeks for 11.7 per cent (234) of the 2,026 patients (excluding 20 patients who aborted) delivered at Vanderbilt University Hospital. Of the remaining patients, 88.3 per cent (1,774) had calculated gestations equal to or longer than 38 weeks, and 18 patients had unknown or unrecorded periods of gestation.

The onset of labor was spontaneous in 92.5 per cent (1,875) of the cases. In the remaining 7.5 per cent (151) of patients, induction of various types or elective termination by cesarean section was carried out. The incidence of induction was equal in the two groups with gestation periods less than 38 weeks and those with longer gestation periods.

Table VI summarizes the duration of labor of the 2,026 patients and compares the duration in the primigravidas with that in the multigravidas. Labors exceeding 20 hours in duration occurred in 11.6 per cent (227) of the cases, with an incidence of 21.9 per cent for primigravidas and 6.8 per cent for multigravidas. Two-thirds of the primigravidas had labors under 20 hours, whereas two-thirds of the multigravidas had labors under 10 hours in duration.

TABLE VI. DURATION OF LABOR IN 2,026 PATIENTS (EXCLUDING 20 ABORTIONS)

TIME	TOTAL NUMBER	PRIMIGRAVIDAS	MULTIGRAVIDAS
< 2 hours	58 (3.0%)	1 (0.2%)	57 (4.4%)
2-9 hours	1,097 (56.6%)	248 (39.4%)	849 (65.0%)
10-19 hours	555 (28.7%)	243 (38.6%)	312 (23.9%)
20-29 hours	142 (7.3%)	82 (13.0%)	60 (4.6%)
≥ 30 hours	85 (4.4%)	56 (8.9%)	29 (2.2%)
Total of known	1,937 (100%)	630 (100%)	1,307 (100%)
Unknown	89 (4.4% of 2,026)	28 (4.3% of 658)	61 (4.5% of1,368)
Grand total	2,026	658	1,368

Vaginal delivery occurred in 96.8 per cent (1,961) of the 2,026 patients (Table VII); the incidence of breech delivery was 3.9 per cent and of midforceps delivery 1.3 per cent. Of the 65 (3.2 per cent) cesarean sections, 27 were repeat sections and 38 were primary. Primary sections were performed in 13 cases for nonobstetric indications (5 cases of diabetes, 5 of active tuberculosis, and 3 for miscellaneous conditions). In the 25 instances with obstetric indications, cephalopelvic disproportion occurred in 16; third trimester bleeding (placenta previa and premature separation of the placenta) in 5; eclampsia 1; uterine inertia 1; and malpresentation 2.

TABLE VII. TYPE OF DELIVERY OF 2,026 PATIENTS (EXCLUDING 20 ABORTIONS)

Spontaneous		1,001 (49.4%)
Low forceps		851 (42.0%)
Midforceps		27 (1.3%)
Breech		79 (3.9%)
Version		3 (0.2%)
Total vaginal deliveries		1,961 (96.8%)
Cesarean sections		65 (3.2%)
Classical	3	
Low transverse	59	
Other	3	
Total		2,026 (100%)

TABLE VIII. COMPLICATIONS OF LABOR AND DELIVERY IN 2,046 PATIENTS

No complications of labor	1,871 (92.4%)
Placenta previa	7 (0.4%)
Premature separation of placenta	24 (1.2%)
Cephalopelvic disproportion	35 (1.7%)
Uterine inertia	9 (0.4%)
Abnormalities of cord, prolapse, etc.	41 (2.0%)
Retained placenta	33 (1.6%)
Miscellaneous	8 (0.4%)
Total complications	2,028 (100%)
Unknown patients	20 (1% of 2,046)
Grand total patients	2,046

In 1,871 (92.4 per cent) patients there were no complications during labor or delivery. The abnormalities which occurred in the remaining 7.6 per cent of the patients are listed in Table VIII. It should be noted that of the 35 cases of cephalopelvic disproportion, only 16 came to cesarean section, and only one of 9 patients with uterine inertia required a cesarean section.

No anesthesia was used in 124 (6.1 per cent) patients. Of the remaining 1,922 patients, 82.5 per cent were given inhalation anesthesia (nitrous oxide, oxygen, and/or ether), 4.5 per cent received pudendal block, 17.1 per cent regional block (spinal, caudal, or saddle block), and 0.3 per cent miscellaneous types. (A few patients had more than one anesthetic per delivery.)

There were no maternal deaths. Postpartum hemorrhage occurred in 1.0 per cent (21) of the cases; this may be compared with an incidence of 9.2 per cent reported by Ebbs, Tisdall, and Scott[1] (Table XII). Puerperal complications occurred in 265 (13.0 per cent) patients (Table IX). Clinical evidence of infection of the reproductive, urinary, or respiratory tract, and so forth, without an oral temperature of 100.4° F. for two readings on successive days post partum (excluding the first 24 hours), occurred in 155 (7.6 per cent) patients. There were 110 (5.4 per cent) patients who had true puerperal morbidity. Only one-half of this morbidity could be accounted for on the basis of reproductive-tract infection. The incidence of puerperal morbidity of 5.4 per cent in our series is but half that of 12.6 per cent as experienced in the series of 400 patients reported by Ebbs, Tisdall, and Scott[1] (see Table XII).

TABLE IX. COMPLICATIONS* OF PUERPERIUM IN 2,026 PATIENTS (EXCLUDING 20 ABORTIONS)

	NO FEVER	WITH FEVER	TOTAL
Infection of the reproductive tract	59	57	116
Infection of breast	2	4	6
Infection of genitourinary tract	48	31	79
Infection of gastrointestinal tract	6	1	7
Infection of upper respiratory tract	14	14	28
Thrombophlebitis	8	5	13
Anemia	13	3	16
Other	8	2	10
Unknown	1	3	4
Total cases	155 (7.6%)	110 (5.4%)	265 (13.0%)

*Included are 21 (1%) patients with postpartum hemorrhage. Numbers within table slightly exceed totals, due to joint complications.

The fetal outcome of 2,048 infants (excluding 20 abortions) is shown in Table X. The absolute fetal loss was 72 in 2,048 (3.5 per cent) or 35 per 1,000 total births. In the immature group, weighing between 400 and 1,000 grams, 14 infants were delivered, all of whom were stillborn or died during the neonatal period. Among the 125 premature infants that weighed from 1,000 to 2,500 grams, there were 27 stillbirths or neonatal deaths. In this group the fetal loss was 21.6 per cent, or 216 per 1,000 total births. This compares with a fetal loss of 1.6 per cent or 16 per 1,000 total births of infants that weighed over 2,500 grams. Our absolute fetal loss of 3.5 per cent may be compared with that of Burke and co-workers,[2] 3.2 per cent, of Smith,[4] 5.6 per cent, and of Williams and Fralin,[3] 3.6 per cent (see Table XII).

TABLE X. FETAL OUTCOME OF 2,048 INFANTS (EXCLUDING 20 ABORTIONS)

WEIGHT	TOTAL NUMBER	NUMBER OF			
		LIVEBIRTHS	STILLBIRTHS	NEONATAL DEATHS	TOTAL FETAL LOSSES
400- 999 grams	14 (0.7%)	10	4	10	14
1,000-2,499 grams	125 (6.0%)	113	12	15	27
2,500 grams or more	1,909 (93.3%)	1,895	14	17	31
Total	2,048 (100%)	2,018	30	42	72

Sixteen of the 30 stillborn infants weighed less than 2,500 grams. In 22 cases the cause of the stillbirth could be attributed directly to maternal (diabetes, Rh incompatibility, and other miscellaneous conditions) or obstetric complications (birth trauma, uterine hemorrhage, prolapsed cord, and other miscellaneous conditions). In the remaining 8 cases, one was due to congenital malformations, and in the others there were no obvious maternal or obstetric causes. Twenty-five of the 42 neonatal deaths were of infants that weighed less than 2,500 grams. In 9 cases an obstetric complication contributed to the neonatal death (eclampsia 1, labor complications 4, uterine hemorrhages 4). The causes of neonatal death were abnormal pulmonary ventilation 17; birth injuries 5; congenital malformations 9; infection 5; erythroblastosis fetalis 4; hemorrhagic disease of the newborn 1; undetermined 1.

Congenital malformations were present in 2.6 per cent (55) of the 2,048 infants delivered. These were distributed in equal proportions between primigravidas (2.6 per cent) and multigravidas (2.6 per cent). Only 11 of the infants had malformations that were incompatible with intrauterine or extrauterine life.

Of the 2,018 liveborn infants (excluding 20 abortions and 30 stillbirths) 71.4 per cent (1,417) were completely breast fed at the time of discharge from the hospital (Table XI). Of the remainder, 8.4 per cent (166) were fed solely by artificial means from time of birth.

TABLE XI. FEEDING OF 2,018 INFANTS PRIOR TO DISCHARGE FROM HOSPITAL (EXCLUDING 20 ABORTIONS AND 30 STILLBIRTHS)

Breast feeding	1,417 (71.4%)
Breast feeding and artificial supplementation	401 (20.2%)
Artificial feeding	166 (8.4%)
Total	1,984 (100%)
Unknown	34 (1.7% of 2,018)
Grand total	2,018

It must be kept in mind that obstetric conditions, normal or abnormal, in our series are in a group of 2,046 women who had their complete prenatal and obstetric care in the Vanderbilt University Hospital. These incidences may differ from the commonly accepted incidences of other hospital services which are reported on the whole service experience, rather than only on patients who receive their full care at a given institution. A comparison of obstetric and fetal complications, reported in other studies, the Vanderbilt study,

and standard textbooks is tabulated in Table XII. It is interesting that the Vanderbilt results parallel very closely widely accepted textbook or United States figures, except in spontaneously occurring abortions.

TABLE XII. COMPARISON OF PERCENTAGE INCIDENCE OF SOME OBSTETRIC COMPLICATIONS IN SEVERAL REPORTED SERIES

INCIDENCE OF	I	II	III	IV	V	VI
Anemia	10%	11.3%	22%	5%	–	–
Pre-eclampsia	6-7%	4.5%	4.8-5.7%	13.0%	4.1%[c]	3.8%
Eclampsia	0.7%	0.5%	–	–	–	–
Placenta previa	0.5-1.0%	0.4%	4.5%	1.9%	–	–
Premature separation of placenta	0.3-1.0%	1.2%		–	–	–
Abortions, spontaneous	10%	4.4%	–	0	–	5.6%
Prematurity	6-12%	6.7%	4.5%	4.2%	7.5%[d]	5.2%
Twins	1.2%	1.1%	–	–	–	–
Breech presentation	3.0+%	3.9%	–	2.8%	–	–
Cesarean section	2.0%[a]	3.2%	–	5.1%	–	–
Postpartum hemorrhage	1-6%	1.0%	9.2%	2.3%	–	–
Puerperal morbidity	–	5.4%	–	13.0%	–	–
Congenital malformations	2.3-3.0%	2.6%	–	–	–	1.4%
Stillbirths/100 total births	1.84%[b]	1.5%	1.3%	2.3%	2.3%	3.0%
Neonatal deaths/100 total births	2.12%[b]	2.0%	–	–	–	2.6%
Breast feeding	65-80%	71%	87%	–	–	–

I. Widely accepted national or textbook figures ([a]United States average, estimated in 1949; [b]United States average rate for whites from 1946 to 1950).
II. Vanderbilt Cooperative Study.
III. Ebbs, Tisdall, and Scott[1] (calculated average for total group).
IV. Burke et al.[2] (calculated average for total group).
V. Tompkins and Wiehl[6] ([c]calculated average for control group of 170 patients; [d]calculated average for total group of patients).
VI. Smith[4] (calculated average for 3 groups, excluding hunger group).

When our results are compared with those of other authors, some variations are noted. The studies of Ebbs, Burke, and Tompkins were carried out in selected groups of patients where larger groups were available for study and so unintentionally they show some degree of bias. Ebbs, Tisdall, and Scott[1] report a higher incidence of anemia, third-trimester and postpartum bleeding, and a lower incidence of prematurity and stillbirths. However, during the past 10 years the definitions of stillbirth and miscarriage have changed and this may in part account for the differences. Burke and associates[2] showed a high incidence of toxemia, puerperal morbidity, and cesarean section. Modern antibiotic therapy has changed the incidence of puerperal morbidity. In our own series less than 50 per cent of the patients with puerperal complications showed a febrile response serious enough to be classified as morbidity. The remaining results are in general agreement, and are within the expected range in all the studies.

As anticipated, there were present interrelationships between obstetric and fetal complications. A given obstetric abnormality was associated in many instances with other obstetric difficulties, and these terminated frequently in abnormal fetal issue. Similarly, an abnormal fetal product was associated with resultant obstetric complications. Some examples of these correlations are:

1. Toxemia.—There were 2 fetal losses among the 10 eclamptic patients, and an increased incidence of pregnancy disease, prematurity, and stillbirths among the 93 pre-eclamptic patients.

2. Fetal Loss.—Associated pregnancy disease and toxemia had a stillbirth rate greater than that of the total group. As expected, prematurity and congenital malformations contributed to an increased neonatal mortality.

3. Prematurity.—There was an increased incidence of prematurity associated with pregnancy disease, pre-eclampsia, neonatal deaths, congenital malformations, and twins.

4. Third Trimester Bleeding.—Stillbirths and neonatal deaths were elevated among patients with premature separation of the placenta. The total fetal loss in this group amounted to over 50 per cent. However, in only 15 per cent of the patients with premature separation of the placenta was there concomitant toxemia.

5. Other Labor Complications.—Fetal loss was increased above the expected rate in prolapse of the cord, cesarean section, breech and version. Among the 227 patients with calculated durations of labor exceeding 20 hours, the neonatal death rate was significantly lower than expected, while the stillbirth rate was unchanged.

It is apparent that the effects of nutrition on any one of these undesirable pregnancy complications must take into account the interrelationship of these abnormalities within the obstetric and pediatric episodes.

Summary

1. A brief outline of the purpose and plan of the Vanderbilt Cooperative Study of Maternal and Infant Nutrition is given.

2. The sample is 2,046 patients who had their complete prenatal and obstetric care at the Vanderbilt University Hospital. This is the total available material from 1945 to 1950.

3. The economic status of these patients was in the low to moderate income range.

4. The results of the prenatal and obstetric course of the 2,046 patients are reported, with comparison with generally accepted textbook incidences and also with incidences in representative previous nutritional studies.

References

1. Ebbs, J. H., Tisdall, F. F., and Scott, W. A.: J. Nutrition **22:** 515, 1941.
2. Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C.: Am. J. Obst. & Gynec. **46:** 38, 1943.
3. Williams, P. F., and Fralin, F. G.: Am. J. Obst. & Gynec. **43:** 1, 1942.
4. Smith, C. A.: J. Pediat. **30:** 229, 1947.
5. Darby, W. J., Densen, P. M., Cannon, R. O., Bridgforth, E. B., Martin, M. P., Kaser, M. M., Peterson, J. C., Christie, A., Frye, W. W., Justus, K., McClellan, G. S., Williams, C., Ogle, P. J., Hahn, P. F., Sheppard, C. W., Carothers, E. L., and Newbill, J. A.: J. Nutrition (in press).
6. Tompkins, W. T., and Wiehl, D. G.: Am. J. Obst. & Gynec. **62:** 898, 1951.
7. Bethell, F. H., Blecha, E., and Van Sant, J. H.: J. Am. Dietet. A. **19:** 165, 1943.

THE VANDERBILT COOPERATIVE STUDY OF MATERNAL AND INFANT NUTRITION*

VI. Relationship of Obstetric Performance to Nutrition

WILLIAM J. MCGANITY, M.D., RICHARD O. CANNON, M.D., EDWIN B. BRIDGFORTH, A.B., MARGARET P. MARTIN, PH.D., PAUL M. DENSEN, SC.D.,** JOSEPHINE A. NEWBILL, B.S., G. SYDNEY MCCLELLAN, M.D., AMOS CHRISTIE, M.D., J. CYRIL PETERSON, M.D.,*** AND WILLIAM J. DARBY, M.D., PH.D., NASHVILLE, TENN.

(From the Division of Nutrition of the Departments of Biochemistry and Medicine, the Departments of Preventive Medicine, Obstetrics and Gynecology, and Pediatrics and the Tennessee-Vanderbilt Nutrition Project, Vanderbilt University School of Medicine)

THE plan and methods of study in this investigation of the relationship of maternal nutrition to obstetric performance have been presented.[1, 2, 3] The obstetric and nutritional characteristics of the sample are described in the preceding reports. This paper summarizes the nutritional characteristics of the several obstetrically interesting groups and compares the findings within these groups to those of the total sample.

It seemed logical to reason that when gestation was uneventful minor aberrations in the over-all nutritional status of the mother were of no real importance. In the abnormal conditions, however, evaluation of nutritional status deserved a most detailed consideration. Ten to 15 per cent of our obstetric patients had one or more complications arise during pregnancy, delivery, or the puerperium. As noted previously,[3] this incidence is approximately that commonly observed in such a population.

Twenty-five abnormal conditions associated with maternal and fetal aspects of gestation have been studied (Table I). Each of these was examined to ascertain any possible differences in nutritional status that may have existed between patients with these conditions and patients in the total group of 2,046 women. The nutritional comparisons were based on dietary intake, laboratory findings, and nutritional physical examination as detailed in another report.[1] It should be borne in mind that these examinations were made as each pregnancy progressed and, therefore, are studies of the patient *before* the obstetric or fetal complication developed or was recognized. None of our appraisal data were of the "recall" type. There was no known bias of *ipso facto* selection. The data include all of the 2,046 patients observed throughout pregnancy and delivery.

*Financial assistance which has made possible this program has been generously provided by grants from the following organizations: the Nutrition Foundation, Inc., the International Health Division of The Rockefeller Foundation, the United States Public Health Service (RG-278 through RG-A-4 [C-6]), the Tennessee Department of Public Health, and Distillation Products, Inc.

**Present address: Department of Biostatistics, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, Pa.

***Present address: Department of Pediatrics, Marquette University, Milwaukee, Wis.

TABLE I. ENUMERATION OF 25 ABNORMAL OBSTETRIC AND FETAL CONDITIONS AMONG 2,046 WOMEN

a. Pregnancy disease in general: miscellaneous group of 6 system conditions, occurring on 225 occasions, associated with the obstetric interlude (Table III of McGanity et al.[3]).
b. Chronic lung disease: 23 patients with active or quiescent tuberculosis of lung in the present pregnancy.
c. Diffuse nontoxic goiter: 13 cases.
d. Diabetes: 7 cases requiring medical management during gestational period.
e. Heart disease: 11 cases of rheumatic heart disease (excluding 10 cases of hypertensive cardiovascular disease).
f. Anemia: 232 patients who had hemoglobin of less than 10 Gm./100 ml. on any occasion during prenatal or puerperal period.
g. Anemia (post partum): 23 patients who had hemoglobin below 10 Gm/100 ml. at postpartum examination.
h. Hyperemesis: 15 patients with severe nausea and vomiting during first trimester of pregnancy, requiring hospitalization.
i. Pre-eclampsia: 93 cases in which sustained hypertension and significant proteinuria, and/or edema developed after the twenty-fourth week of pregnancy in a previously normal gravid woman. Although it is most commonly a disease of the last trimester, it may rarely occur prior to the twenty-fourth week.
Eclampsia: 10 cases in which convulsions and/or coma developed in the pregnant or puerperal woman superimposed on the signs of pre-eclampsia.
j. Placenta previa: 7 cases with varying degrees of lower uterine segment implantation of placenta.
k. Premature separation of normally implanted placenta: 24 cases.
l. Length of gestation at delivery less than 38 weeks: 234 cases calculated on basis of expected date of confinement.
m. Duration of labor equal to or greater than 20 hours: 227 cases, length of labor calculated from onset of effacement and dilation of cervix.
n. Delivery complications: type of delivery other than spontaneous, low forceps, or cesarean section.
o. Cesarean section: 65 cases, 27 repeat, 38 primary.
p. Labor complications: 126 complications in 123 women listed in Table VIII of McGanity et al.,[3] excluding placenta previa and premature separation of placenta.
q. Postpartum hemorrhage: 21 cases with blood loss during or following delivery estimated to exceed 500 ml.
r. Abortions: 20 fetuses of less than 400 grams in weight, 28 cm. in length, and 20 weeks of gestation.
s. Prematurity: 115 liveborn infants that weighed between 400 and 2,500 grams.
t. Twins: 44 infants of 22 mothers (associated prematurity in 23 of these infants).
u. Congenital malformations: 55 infants with valid defects as noted by the pediatrician.
v. Stillbirths and neonatal deaths: 30 stillborn infants and 42 liveborn infants who succumbed during their hospital stay.
w. Puerperal complications: 265 cases of diagnosed puerperal conditions with and without febrile response sufficient to be classified as puerperal morbidity (Table IX of McGanity et al.[3]).
x. Puerperal morbidity: 110 patients who had an oral temperature of 100.4° F. for two readings on successive days post partum (excluding the first 24 hours).
y. Mothers who did not nurse: 243 patients who had single live births and postpartum checkups, who were not nursing infants on hospital discharge.

In order to determine whether deviations occurred in the abnormal obstetric groups, we must characterize those changes which are usual physiologic adjustments during the reproductive interlude. Many of these changes have been individually reported by other workers. (See, for example, the review by Toverud, Stearns, and Macy.[4]) In the present study, these changes have been observed simultaneously for the first time and so there exists the possibility of evaluating the interrelation of nutrient intake and biochemical measurements in a large group. In both the laboratory and dietary results, the distributions of a few variables were sufficiently skewed that the reporting of mean values is not informative. These skewed distributions are represented by the median, tenth and ninetieth percentile values. The mean or median values of

dietary and laboratory data for the total group, by trimester, are given in Tables II and III. These gross levels are influenced by such factors as season, age, parity, and trimester of entry into the study of the mother, all of which have been[2] or will be discussed in other publications.

TABLE II. SUMMARY OF DAILY NUTRIENT INTAKES FOR EACH TRIMESTER

NUMBER OF DIET RECORDS	FIRST TRIMESTER 278			SECOND TRIMESTER 1,222			THIRD TRIMESTER 1,665		
NUTRIENT	MEAN	S.D.		MEAN	S.D.		MEAN	S.D.	
Total calories	2,140	630		2,200	630		2,020	640	
Protein (Gm.)	75	22		75	21		70	21	
Percentage animal protein	66	9		65	10		65	10	
Calcium	1.1	.4		1.1	.4		1.0	.4	
Iron (mg.)	13	4		14	4		13	4	
Thiamine (mg.)	1.5	.5		1.5	.5		1.4	.5	
Niacin (mg.)	12	4		12	4		11	4	
Riboflavin (mg.)	2.5	.9		2.5	.9		2.3	.9	
	P_{10}	MEDIAN	P_{90}	P_{10}	MEDIAN	P_{90}	P_{10}	MEDIAN	P_{90}
Total vitamin A activity (I. U.)	2,700	6,500	13,600	2,800	6,600	13,800	2,400	5,900	13,400
Vitamin C (mg.)	26	66	123	25	62	120	19	55	114
Vitamin D (I. U.)	30	64	100	32	67	107	27	62	101

It is apparent that the average nutrient intakes fell below the Recommended Dietary Allowances of the National Research Council.[5] These were not so disturbingly low as to warrant concern and the range of intakes was sufficiently wide to allow comparisons within our study of the obstetric and fetal performance among groups of women at several levels of intake.

Contrary to tables of recommended standards, there was observed an overall *decrease* in nutrient intake during the third trimester of pregnancy. This might be attributed in part to the advice which physicians often gave to patients in an effort to avoid excessive weight gain during the latter part of pregnancy. On the other hand this may reflect the dietary needs of healthy pregnant women and bear little relation to the physicians' advice.

The detailed nutritional laboratory findings have been reported[2] in four categories:

1. Hematologic values and serum protein concentrations.
2. Fat-soluble vitamins in the blood serum.
3. Serum ascorbic acid levels.
4. Urinary excretion of B vitamins following an oral load test.

There was the expected decrease in hemoglobin concentration, erythrocyte count, and packed cell volume. These decreases in mean values during pregnancy were not associated with changes in the blood indices to an extent that would indicate that they were due to a severe lack of any hemopoietic substances, such as iron, copper, or vitamin B_{12}. Rather, the normochromic, normocytic blood picture reflects mainly the increased blood volume (hemodilution) of pregnancy. Similarly, the decrease in serum total protein and albumin is consistent with the recognized increased plasma volume or hemodilution. All of these values, except hemoglobin and mean corpuscular hemoglobin concentra-

TABLE III. SUMMARY OF LABORATORY DATA FOR EACH TRIMESTER AND POST PARTUM

NUMBER OF LABORATORY DETERMINATIONS	FIRST TRIMESTER 343			SECOND TRIMESTER 1,376			THIRD TRIMESTER 1,974			POST PARTUM 1,553		
	MEAN	S.D.		MEAN	S.D.		MEAN	S.D.		MEAN	S.D.	
Hemoglobin (Gm./100 ml.)	13.02	1.24		12.22	1.20		11.66	1.34		12.98	1.32	
Packed cell volume (%)	38.7	3.2		36.4	3.0		35.3	3.3		40.3	3.1	
MCV (cubic microns)	90.3	8.5		89.7	7.8		89.5	8.4		89.0	8.7	
MCHC (%)	33.61	1.89		33.55	1.87		32.96	2.03		32.25	1.81	
Total serum protein (Gm./100 ml.)	6.89	.45		6.54	.43		6.34	.42		7.14	.47	
Serum albumin (Gm./100 ml.)	4.55	.42		4.24	.39		4.04	.39		4.67	.39	
Serum vitamin A (I.U./100 ml.)	111.	30.		112.	29.		100.	30.		140.	37.	
Serum carotene (μg/100 ml.)	117.	44.		145.	53.		160.	63.		120.	51.	
	P_{10}	MEDIAN	P_{90}	P_{10}	MEDIAN	P_{90}	P_{10}	MEDIAN	P_{90}	P_{10}	MEDIAN	P_{90}
Serum vitamin C (mg./100 ml.)	0.09	0.47	1.11	0.09	0.47	1.00	0.06	0.35	0.95	0.00	0.20	0.77
Urinary thiamine excretion (mg./2 hr.)	.055	0.134	.292	.037	0.115	.243	.020	0.089	.198	.022	0.100	.224
Urinary riboflavin excretion (mg./2 hr.)	0.17	0.86	1.87	0.19	0.85	1.89	0.15	0.72	1.65	0.12	0.61	1.51
Urinary N^1-methylnicotinamide excretion (mg./2 hr.)	3.0	6.6	11.9	3.2	7.9	16.0	3.7	9.6	19.5	2.1	5.2	9.8

tion (MCHC), returned to or exceeded initial levels at the time of the postpartum check. The readjustment of hemoglobin level following delivery was less rapid than the other changes. This was reflected in the mean corpuscular hemoglobin concentration. These findings imply some limitation of hemopoiesis, possibly due to mild iron deficiency in the third trimester and post partum. That these changes are detectable at all is due to the large number of cases available for study. The decrease in MCHC in the third trimester seems to reflect the increased need for iron by the mother during the latter portion of pregnancy, a need which was apparent in the influence of pregnancy upon absorption of this element.[6] The more pronounced decrease apparent during the puerperium is, in all likelihood, the result of the blood loss occurring during or following delivery.

Low values of serum vitamin A are more frequently encountered in pregnant than in nonpregnant women. A downward trend in concentration of this vitamin in the serum commenced early in gestation and reached its maximum depression in the third trimester. Normal nonpregnant values were again attained by the six weeks post partum visit. By contrast, the concentration of carotene and tocopherol in the serum rose progressively during pregnancy and reverted to initial values post partum. Alterations in dietary intake do not account for these changes in serum carotene and tocopherol. These phenomena suggest that the lipid-transporting ability of the serum is increased during pregnancy, paralleling the known increase in serum cholesterol.[7]

Serum ascorbic acid concentrations decreased slightly during gestation. A sharp decrease occurred post partum in the group of women who were breast feeding their infants. Mothers of artificially fed infants did not exhibit a further decline in their levels. During the gestational phase, the distributions of serum levels of ascorbic acid revealed a considerable number of values below 0.2 mg./100 ml. But the over-all distribution, if found in nonpregnant individuals, would not be viewed with alarm. The general pattern of serum levels would certainly not be associated with definite clinical evidence of vitamin C deficiency, and no such physical signs were seen in our group of 2,046 patients.

B-vitamin excretions varied during pregnancy. A slight decrease occurred in the median thiamine and riboflavin excretions during the period of gestation. By contrast, the N^1-methylnicotinamide excretion rose progressively, attaining, during the third trimester, values approximately twice the nonpregnant (postpartum) ones. Even though the metabolic causes of these variations are not known, they have to be recognized in analyzing for significance the associations between nutriture and quality of pregnancy.

Physical evidence of frank deficiency disease was entirely absent from the study group.[2] Not one examiner found a single case of scurvy, beriberi, pellagra, or other deficiency syndromes. The commonest diagnosis of nutritional disease was obesity, which was recorded in 15.8 per cent of all examinations. In the realm of so-called "subclinical" signs of dietary deficiency, extreme inconsistencies between examiners emphasized the nebulous nature of many of the proposed stigmas. However, the recording of these "subclinical" signs could be directly related to four factors:

1. Age and Parity.—With increasing age and/or parity there were increases in the recorded incidence of skin, oral, lingual, ocular, and gingival lesions, obesity, edema, and varicosities. These trends were present after the first baby, but were more evident after three or more children.

2. Season.—Disorders of the skin, gingivae, eyes, nose, mouth, and edema showed seasonal variations.

3. Trimester.—The incidence of obesity, gingival lesions, edema, and varicose veins increased with advancing pregnancy, while dermatologic signs and lingual changes decreased post partum. All of these phenomena, except the somewhat borderline increase of gingival lesions, may be explained as normal, physiologic changes of the obstetrical episode.

4. Examiners.—The major factor which influenced the recording of physical signs of "subclinical" deficiency was the variation among examiners. A great many apparent seasonal variations and trimester trends were artifacts produced by observer differences. When frank nutritional disease is in evidence, we may hope for considerable uniformity in appraisal by physicians. When the objective evidence is less definite, however, examiner judgment becomes the determining factor in the diagnosis of a "subclinical" deficiency state.

Method of Analysis

The whole experience of the 2,046 patients was summarized as the total group. The twenty-five subgroups (Table I) with obstetrical and fetal complications were then compared with this total group for each of the dietary and laboratory measurements (Appendix Tables I and II).

For these comparisons the method of Schrek[8] was used. This allows for an immediate visual appraisal of the likelihood of a single subgroup differing significantly from the experience of the total group. For this comparison funnel-type curves (Fig. 1) were constructed, with two bands delineating the 1 per cent and 5 per cent levels of significance. The mean value for the total group is the horizontal line bisecting the funnel. The abscissa is scaled for the number of cases in the subgroup, and the ordinate for positive or negative deviations of the mean of the subgroup from the mean of the total group. Increasing numbers of cases in a subgroup result in reducing the deviation from the total mean which is required to produce a significant difference. This technique is simply the statistical procedure known as the t-test which is widely used for the comparison of average levels in pairs of samples. Data of skewed distribution have been evaluated in this manner by comparison of proportions falling below certain levels; the technique is a graphical application of the procedure known as the chi-square test. This method of analysis has the advantages of permitting more rapid comparisons of characteristics of small groups of varying size, and of allowing compact visual presentation of many such comparisons.

Fig. 1 illustrates this approach. The upper right graph shows arithmetic levels of hemoglobin during the third trimester, with deviations of subgroups scaled in terms of actual values. Only the "anemia groups" (selected by the attribute of a hemoglobin level of less than 10 Gm./100 ml.) and the subgroup with puerperal complications deviate from the mean of the total experience to such an extent as to be significant at the probability level of 0.01. Mothers who had twin pregnancies or puerperal complications had hemoglobin levels below

the mean of the whole, sufficient to be classified as of borderline significance. Mothers who gave birth to premature infants and those who did not nurse their infants exhibited hemoglobin concentrations higher than expected, but at a level of borderline significance. The second row of graphs shows blood hemoglobin concentrations and dietary iron intakes, using a coded vertical scale to allow data for different phases of gestation to be shown on the same chart. All hemoglobin points for which any sample value showed a significant deviation are identified by a letter, and these points and any significant iron values are plotted on the iron-intake chart. Throughout the remainder of the charts a given measurement for each of the 25 subgroups is compared with the total experience at the appropriate pregnancy interval. However, the measurements which did not differ importantly from the whole group experience are not depicted. This omission is for clarity of visual presentation. The third row of charts shows coded mean serum total protein levels and protein intakes for all groups. The bottom row compares proportions of cases below indicated levels of serum vitamin C and vitamin C intakes. This visual presentation emphasizes that when many hundreds of statistical tests are applied, random sampling variation is expected to produce some significantly deviated results in the sampling of subsamples from the same population. The number of "significant" differences will depend upon the limits of significance decided upon by the investigator (i.e., the width of the funnel). Obviously, every point which falls outside the limits on our charts is not necessarily actually different from the mean of the whole population.

Tables I and II of the appendix give the comparative differences of the subgroups from the total group on the arithmetical basis of their dietary and laboratory data. The significant variations from the total group are marked by a series of asterisks (one asterisk denoting a significance of 5 per cent, two asterisks 1 per cent, and three asterisks a significance of 0.1 per cent). This table permits one to appraise the magnitude of the observed differences between groups, the difficulty of detection of the deviation in individual patients, and the possible physiologic meaning of these differences. The degree of significance is sometimes statistically large, where the arithmetical difference involved is quite small. In no case, except the elevated serum carotene levels of diabetic patients, was there a clear separation of the distributions of any variable for a studied subgroup from that of the total group. The differences observed are slight shifts in mean levels, with large bands of overlap. Where meaningful significance exists between the groups, it is demonstrable because of the large number of cases. Indeed, it would be fallacious to individualize any result and hope to transpose it to an individual patient.

Results

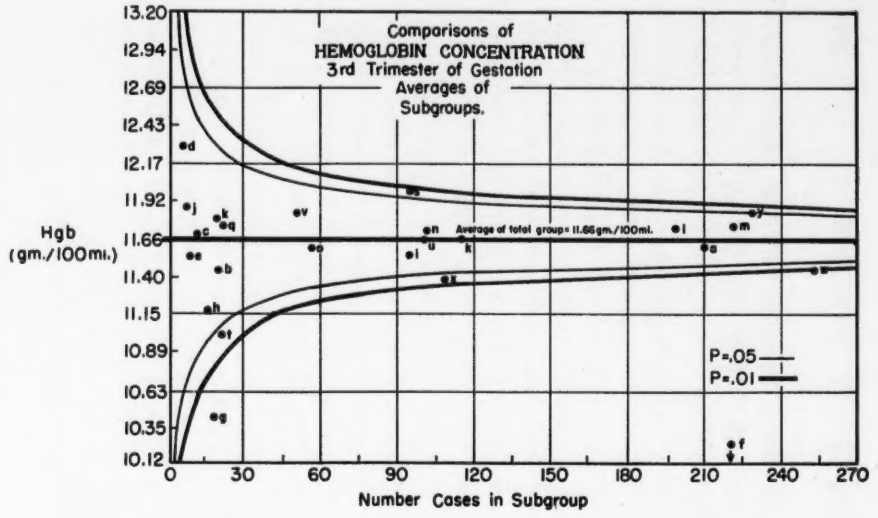
A. Laboratory, Nutrient, and Physical Findings in the 25 Subgroups With Obstetrical and Fetal Abnormalities.—

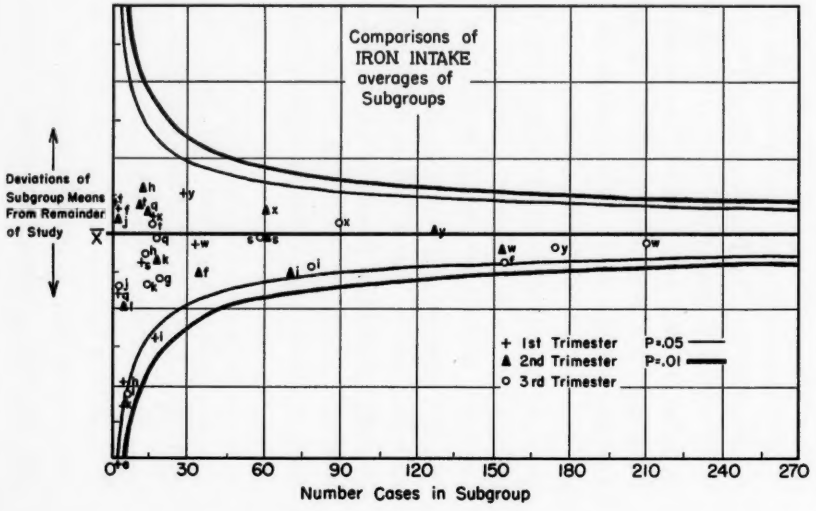
Those subgroups with characteristics differing from the pattern of the total group are:

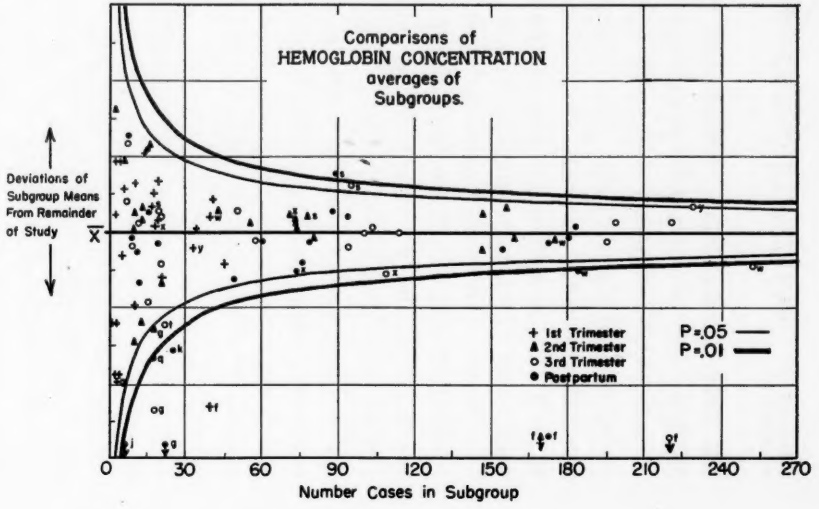
1. Pregnancy disease in general: The six conditions listed in Table III of the preceding paper[3] comprise a miscellaneous grouping of primarily medical

LEGEND

a Pregnancy disease in general
b Chronic lung disease
c Diffuse nontoxic goiter
d Diabetes Mellitus
e Heart disease
f Anemia (<10 gm. Hb) on any occasion
g Anemia (< 10 gm. Hb) postpartum
h Hyperemesis
i Pre-eclampsia or eclampsia
j Placenta previa
k Premature separation of placenta
l Weeks gestation at delivery < 38 wk.
m Duration of labor ≥ 20 hr.
n Delivery complications
o Cesarean section
p Labor complications, not j or k
q Postpartum hemorrhage
r Abortions in hospital
s Prematures (<2500 gm. birth wt.)
t Twins
u Congenital malformations
v Stillbirths and neonatal deaths
w Puerperal complications
x Puerperal morbidity
y Mothers who did not nurse







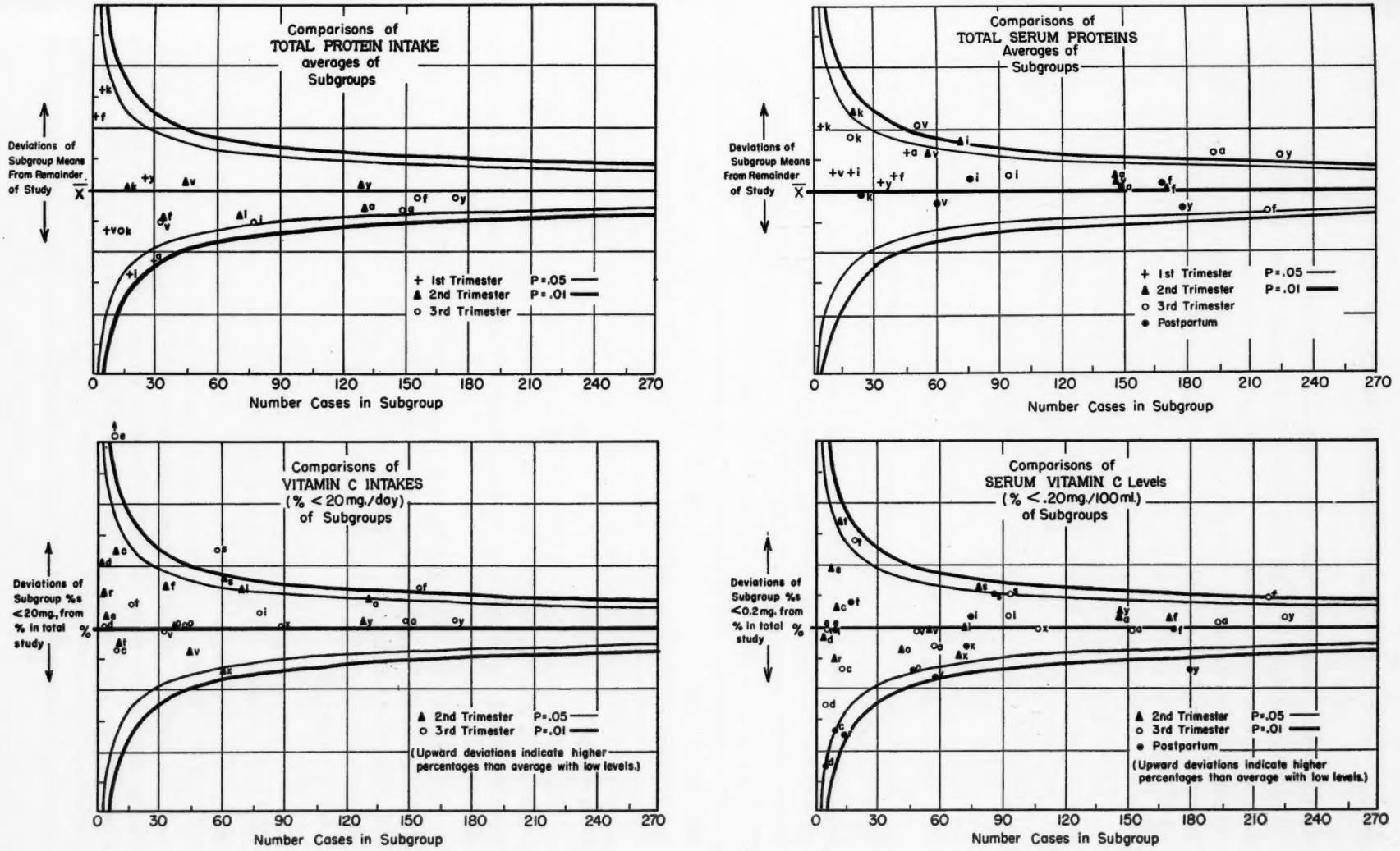


Fig. 1.—Method of comparison of subgroup averages with total groups (see text, page 506).

complications associated with the gestational episode. The conditions are a heterogenous mixture of several systemic diseases. Some of these contribute more to significant abnormalities in nutritional status than others. For instance, chronic lung disease and nontoxic goiter revealed no significant deviations in nutrient intake, laboratory data, or physical examination that would separate them from the characteristics of the total study group. By contrast, heart disease and diabetes did produce significant variation.

In the group of women with these conditions there was recorded a general lowering of nutrient intake throughout pregnancy, most pronounced during the first trimester. This decrease was significant for total calories, protein, calcium, and riboflavin, and was at a level approximately 10 per cent lower than that of the total group. The dietary intake of vitamin C was slightly lower in the second trimester, while the niacin intake in the third trimester was also low. In no instance did the mean or median values approach critical levels.

There was little evidence of meaningful deviation of the laboratory findings from the total group. Serum levels of vitamin C were lowered only in the first trimester. However, the median level of 0.34 mg./100 ml. is not such as to be considered indicative of deficiency disease. A significant elevation of total serum protein concentration was detected in the third trimester, followed by a reduction of serum albumin concentration post partum. The total serum protein values tended to be above the average throughout pregnancy, but to a level of significance only in the third trimester. No explanation can be offered. There was not a corresponding elevation of protein intake, and the hemotologic values were not such as to confirm a generalized hemoconcentration effect. Serum vitamin A levels were slightly but significantly elevated at the postpartum examination.

These deviations in nutrient and laboratory data were not accompanied by physical signs of deficiency. The only significant physical stigmas, in these patients, was a recorded increased incidence of edema on postpartum examination.

One must keep in mind that the numbers of patients observed are small, especially in the first trimester. (See Appendix Tables I and II.) Also, the deviations from the values of the total study group are minimal—at most a 10 per cent elevation or decline—and on an individual basis would not be considered important.

2. Heart disease: Eleven patients had rheumatic cardiovascular disease (Table III of preceding paper[3]) of varying degrees of severity. None was of such severity—Grade III or IV cardiac—as to warrant consideration of therapeutic abortion.

The nutrient intake of these patients seemed to be slightly lower than that of the total study group throughout the whole of pregnancy. It is the clinic policy in the treatment of patients with heart disease to attempt strict dietary control, to avoid excessive weight gain and to reduce obesity. The general lowering in dietary intake thus seems to be a reflection of the physicians' advice.

Only in the third trimester was lowering of nutrients (vitamins A and C, and iron) significant. The decreases in these latter nutrients were appreciable. (See Appendix Table I.)

Study of the physical examinations revealed that this small group of women was divided between the two extremes of underweight and overweight and that there was a greater frequency of gingival lesions than might be expected within this group. Although the laboratory values followed a pattern consistent with the other findings, the number of individuals involved and the degrees of deviation were not such as to render them statistically significant.

3. Diabetes mellitus: There were 7 diabetic mothers. Our management of these patients, as with the cardiac patients, necessitates the closest collaboration with the internist as a joint medical problem. Where possible, these pregnancies are electively terminated at about 37 weeks by the appropriate route—either vaginal or abdominal—and the women are not allowed to nurse their infants.

There were no significant deviations from the total study group in the nutrient intake or physical findings.

There was a consistent elevation of serum carotene as early as the second trimester, which persisted through the postpartum examination. This confirms previously reported high serum carotene levels among diabetic individuals[9] As a result of not nursing their infants, the diabetic mothers had significantly elevated serum vitamin C levels at the postpartum examination.

4. Anemia: The clinical diagnosis of "anemia" was made by physicians when the hemoglobin level was less than 10 Gm./100 ml. This diagnosis was made in 232 (11.3 per cent) patients during the prenatal (10.5 per cent) or puerperal phases (0.8 per cent) of gestation. The actual number of cases were 3 during the first, 48 in the second, 165 in the third trimester, and 16 during the postpartum period. Only 35 per cent of the 216 patients who developed "anemia" during the prenatal period received *any* iron supplementation during gestation. In all but 7 instances, the patients with levels below 10 Gm. during pregnancy returned to values above 10 Gm./100 ml. by the time of their postpartum visits. These 7 individuals and the additional 16 who developed "anemia" for the first time post partum, all experienced a postpartum decline in hemoglobin concentration. In 12 instances the "anemia" appearing post partum was associated with either excessive blood loss at the time of delivery or other severe obstetric complications.

Of the 232 "anemic" women, only 37 had indices (MCHC$<$30 and MCV$<$ 75) that would classify the anemia as being due to iron deficiency. One woman with an MCV $>$ 100 was considered to have a mild macrocytic anemia.

As one would expect, the most pronounced differences existing in the laboratory data on the "anemia group" were in hematologic values. These were lower throughout the whole of gestation and were associated with generalized lowering of other blood and serum determinations. This seems to reflect some increase in plasma volume (hemodilution). Significant deviations from the characteristics of the total group were evident in lowered levels of hemoglobin, PCV, MCV, and MCHC and vitamin C as early as the first trimester, but sig-

nificant changes in serum total protein, albumin, and vitamin A were not evident until the second or third trimester. The third trimester observations were made during the mid-portion of the trimester, which corresponds to the occurrence of the peak increase of plasma volume.[10, 11] These relationships will be considered in a more detailed evaluation of the "anemic" group which is now in preparation. The question may be raised, however, as to whether the diagnosis of "anemia" on the basis of hemoglobin of less than 10 Gm./100 ml. is suitable for dealing with obstetric patients, especially during the third trimester.

The mean iron and median vitamin C intakes of the "anemia" group tended to be lower than those of the total group throughout all three trimesters, but were significantly so only in the third trimester. The values for neither approached minimal levels. The other laboratory and nutrient data do not differ consistently for the "anemic" group *in toto* or in any of the four gestational periods tested.

Deviations in physical findings from the total group were evident only during the third trimester, and consisted of a significantly increased frequency of edema (12.0 per cent versus 6.9 per cent) and of abnormalities of the tongue (11.0 per cent versus 6.6 per cent).

5. Toxemia: There were 103 patients classified as exhibiting toxemia, 93 cases of pre-eclampsia and 10 of eclampsia. Fortunately, there were no maternal deaths. Eight of the 72 fetal deaths (11 per cent) in the total study were associated with toxemia in the mother.

The average nutrient intake of these women tended to be lower than that of the total study group throughout the prenatal period, and was significantly so in the first and third trimesters. The recorded intakes of protein, iron, riboflavin, and niacin were lowered significantly during the first trimester. Any interpretation of this lowness should take into consideration possible unrepresentativeness of the relatively small number of toxemic women who had dietary records for the first trimester. Nutrient intake improved during the second trimester and only niacin and vitamin C were significantly lowered. In the third trimester, there was again a general decline in nutrient intake but significantly so only in total calories and niacin.

The laboratory values during the first trimester did not vary from those of the total group. During the second trimester, the data revealed a significant elevation of levels of serum total protein and albumin. This was not associated with elevations of other serum or blood levels consistent with the previously reported[12, 13] hemoconcentration associated with the acute toxemias. There was significant lowness of the MCV and MCHC in the third trimester, but this was not of a degree that could establish clear evidence of iron deficiency. The urinary excretion of N^1-methylnicotinamide tended to be low throughout the prenatal and puerperal periods but was significantly so only in the latter. Whether this reflects the recorded lower niacin intake or some metabolic phenomena cannot be decided for certain.

Only in the absence of obesity and slight increase in the recording of pedal edema were the physical findings in the 10 eclamptic women significantly different from those of the total group of 2,046 patients. On the other hand, among

the 93 pre-eclamptic patients, the incidence of obesity was significantly increased over that of the total group (35.3 per cent against 18.5 per cent). Edema of the lower extremities was also increased significantly in the second and third trimesters, and post partum, being 3 times as prevalent in the pre-eclamptic group as in the total group during each period.

The lower nutrient intake of the women who developed toxemia appears to be a result rather than a cause of the condition. This interpretation is supported by the observations on the pre-eclamptic group in which there was a high incidence of obesity (35.3 per cent in the third trimester, 24.6 per cent post partum) associated with a threefold increase in the expected rate of dependent edema. On clinical grounds, therefore, these patients received physicians' instructions to restrict their nutrient intake. The dietary data indicate that such advice was followed.

6. Puerperal complications and puerperal fever: Two hundred sixty-five (13.0 per cent) patients had puerperal complications. Of this number only 110 (5.4 per cent) had a sufficient febrile response to be classified as having puerperal morbidity. As mentioned in the preceding paper, only one-half of this morbidity was associated with reproductive-tract infection (Table IX of the preceding paper[3]).

In neither group (265 or 110) were there any general or significant trends in nutrient intake that were different from the values of the total study group. Similarly there was no evidence of any stigmas of nutritional disease recorded on physical examination.

However, in spite of consistently adequate intakes of iron and vitamin A throughout the whole pregnancy interlude, hematologic and serum vitamin A levels were significantly lowered. In both instances this revealed itself early in the second trimester and persisted through the postpartum examination. Hemoglobin, MCV, and MCHC values were not altered in a manner to permit the definite conclusion of iron deficiency. Although decreased, the average levels of serum vitamin A remained in excess of 100 I.U./100 ml.

It makes an attractive hypothesis that these lowered values reflect an increased susceptibility to infection during the puerperal period. It is to be recalled that a similar association between hemoglobin levels and puerperal morbidity was observed earlier in our institution.[1] Obviously the magnitude of these hematologic changes is not such that one could individualize in a given patient.

7. Stillbirths and neonatal deaths: Seventy-two infants were stillborn or died during their hospital stay. The 71 mothers of these infants showed no significant deviations in dietary intake from those of the total study group.

There was not a general trend (either elevation or decline) in laboratory data. However, serum total protein and albumin tended to be elevated throughout the prenatal period, but were significantly so only in the third trimester for the mothers of stillborn infants and in the second trimester for the mothers of infants who died during their hospital stay. One might postulate that this finding reflected the toxemic patients in this group. This is not the case, however, since acute toxemia was associated in only 11 per cent of the fetal loss. As a

result of the failure to nurse the infants, this whole group of mothers exhibited the expected significant postpartum elevation of serum vitamin C. The serum carotene levels had not returned to normal values.

No significant increase in the incidence of physical stigmas was recorded against the 41 mothers whose infants died during the neonatal period. However, among the 30 mothers who had stillbirths, there was a significant twofold increase in the recording of obesity and of pyorrhea over the characteristics of the total group.

8. Premature infants: There were 123 liveborn infants of 115 mothers with birth weights between 400 and 2,500 grams. As mentioned before, a 100 per cent fetal loss occurred in the group under 1,000 grams, whereas, between 1,000 and 2,500 grams, the loss was 21.6 per cent. The group excludes 16 stillbirths classified as premature.

The nutrient intake of the mothers of these infants was within the range of the total study group, except for vitamin C. A greater number of these patients than expected had an ascorbic acid intake of less than 20 mg. per day in the second and third trimesters.

The laboratory data reflected this change with a significant increase in the number of cases, in the last two trimesters, with levels of serum vitamin C below 0.2 mg./100 ml. In addition, there tended to be elevated hematologic values throughout gestation, but, to a point of significance, only in the third trimester and post partum. These changes affect all four determinations—hemoglobin, PCV, MCV, and MCHC. Serum vitamin A was elevated in the third trimester. The explanations are not apparent.

There was a significant twofold increase in the expected rating of undernutrition on physical examination, but no significant evidence of physical signs of ascorbic acid deficiency to correlate with the nutrient and laboratory data. The actual magnitude of the changes in the median intake and serum level of vitamin C is of a degree that approaches minimal or borderline amounts. If these differences were of physiologic importance, one might have expected some increase in physical evidence of gingival lesions in this subgroup over the total group. No such evidence was observed.

9. Mothers who did not nurse: The reasons for failure of mothers to nurse were varied: (1) lack of desire; (2) insufficient supply of milk with present or previous pregnancies; (3) stillbirths and neonatal deaths; (4) physicians' decisions because of coexisting complications such as diabetes or mastitis. Analysis was made of 243 mothers who were not nursing their infants on hospital discharge, and who had single livebirths and postpartum checkups.

The dietary intakes of these women did not differ significantly from those of their obstetrical sisters in the total study group. In spite of this, there was a trend toward general elevation of the laboratory values in the third trimester, which reached significant levels for hemoglobin, serum total protein, and vitamin A. This is probably due to random variation, as the arithmetical rise (Appendix Table II) is very slight. The serum vitamin C level was elevated post partum. This postpartum laboratory finding of a higher average ascorbic acid content of serum of nonlactating women is a constant finding and reflects decreased maternal requirements and a lack of the lactational drain.

10. Hyperemesis gravidarum: Fifteen patients had nausea and vomiting of pregnancy of such severity as to produce ketosis and require hospitalization. They exhibited but few deviations of laboratory data from the characteristics of the total study group.

In this group, the serum vitamin A levels tended to be elevated throughout the prenatal and puerperal periods, but were significantly so only in the second trimester. This was not associated with any change in serum carotene values. The explanation of this phenomenon is not apparent, but it may possibly be related to hepatic function.

On the postpartum physical examination, two of the fifteen women were recorded as presenting neurological findings. The low incidence (1.5 per cent) of neurological disorders recorded for the total group makes this result appear significantly greater. However, one of these two women had calf tenderness as the sole neurological finding, and this was associated with varicosities and edema. Neither of these subjects exhibited dietary or laboratory evidence of B complex deficiency.

11. Blood loss: Fifty-two patients had excessive loss of blood at delivery or during the puerperal phase, due to placenta previa, premature separation of the placenta, or postartum hemorrhage. Although their nutrient intakes were not significantly different from those of the total study group, these patients had lowered postpartum hematologic values. These deviations occurred in hemoglobin, PCV, and MCHC. For hemoglobin, this mean decline amounted to as much as 1.8 Gm. below the value for the total study group. The etiology of this conditioned iron deficiency is evident.

It is of practical interest that, in spite of what was considered unit-for-unit replacement of blood at the time of these accidents, the subsequent findings indicate an underestimation of blood loss by some 500 c.c.

12. Twins: There were 22 sets of twins delivered during the period of the study. Of the 44 infants, 23 (delivered of 15 mothers) were classified as premature on the basis of a birth weight less than 2,500 grams. The 22 mothers had no variation in dietary intake from that of the total group.

The differences in the mothers with twins and the total group reflected changes in water metabolism. A significant drop in third-trimester hematologic and serum levels amounted to approximately 7 per cent. This appears to reflect an increased hemodilution. In addition, there was a significantly increased incidence of edema among this group during the third trimester.

13. Other conditions: In the conditions listed below no dietary or laboratory findings differentiated the group of patients from their normal obstetrical sisters in the total group:

1. Abortions: 20 patients who had infants that weighed less than 400 grams and were of less than 20 weeks' gestation.
2. Chronic lung disease: 23 cases of quiescent or active tuberculosis associated with the present pregnancy.
3. Primary or repeat cesarean sections: 65 cases.
4. Those patients—not already discussed—who developed obstetric complications prior to, during, or following delivery.

5. Labors exceeding 20 hours in duration: 227 cases.

6. Calculated periods of gestation of less than 38 weeks' duration: 234 cases.

7. Infants with major or minor malformations: 55 cases.

These mothers had no significant deviations in nutrient intake, laboratory data, or physical stigmas that would differentiate them from the total group of 2,046 patients.

B. Maternal and Fetal Complications, Laboratory, and Physical Findings for Women With Unusually High or Low Nutrient Intakes.—

To evaluate further the influence of dietary differences upon the quality of pregnancy we have tabulated characteristics of the 2,046 women with low or high extremes in nutrient intake level. These have been compared on the basis of laboratory data and physical examination, and obstetric and fetal performance. The extremes were chosen on the statistical division of a deviation of greater than one and two standard deviations above or below the mean or the equivalent percentiles of the distribution for skewed values (Table IV). Skewed values pertained for vitamins A and C. The actual figures have been rounded to fit the intervals of our coded material.

It should be noted that, at the level of one standard deviation below the mean, the values for vitamins A, C, thiamine, riboflavin, and niacin would meet the recommended dietary intake for these nutrients during the latter half of pregnancy suggested by the British and Canadian standards.[14, 15] One must keep in mind the arbitrary nature of dietary allowances recommended by any agency and acknowledge that the values tend to be higher than actual minimal maintenance requirements.

TABLE IV. APPROXIMATED* NUTRIENT INTAKES—MEANS OR MEDIANS, AND RANGES†—VANDERBILT COOPERATIVE STUDY, ANY TRIMESTER

NUTRIENT	−2 S.D.	−1 S.D.	MEAN	+1 S.D.	+2 S.D.
Total calories	1,000	1,500	2,100	2,750	3,250
Protein (Gm.)	40	50	72	90	110
Calcium (Gm.)	0.25	0.75	1.10	1.50	2.00
Iron (mg.)	6	10	13.5	18	22
Thiamine (mg.)	0.7	1.0	1.4	1.9	2.2
Riboflavin (mg.)	0.5	1.5	2.5	3.5	4.5
Niacin (mg.)	4.0	8.0	12.0	16.0	20.0
	2½%	16%	MEDIAN	84%	97½%
Vitamin A (I.U.)	1,000	3,000	6,000	11,000	19,000
Vitamin C (mg.)	20	40	60	100	160

*Values are rounded to fit interval groupings of coded material.
†Ranges are 1 and 2 standard deviations about means, or median equivalents.

The detailed analysis of these groups will be presented elsewhere. Suffice it to summarize here the results:

(a) No decrease or increase in obstetric or fetal complications occurred in the group at the higher intake level; that is, an intake level greater than one or two standard deviations above the mean or median for the total group.

(b) A significantly increased incidence of pregnancy diseases in general and of toxemia (pre-eclampsia and eclampsia) was present among the women whose dietary intakes fell approximately one standard deviation or more below

the mean of the total group. However, when the intake level was reduced to two standard deviations or more from the mean of the whole group, the increase was not significant—a reflection of the small subgroups involved.

Comment

There have been presented the obstetric, fetal, nutritional, and physical characteristics of a group of 2,046 women who received their prenatal care at the Vanderbilt University Hospital in the period between 1945 and 1950. Economically, this population would be placed in the low to moderate income groups. It is not the lowest socioeconomic or nutritional stratum of society and we feel that the composition of the group approximates closely the average of obstetric patients encountered in general practice or in hospital clinics. Accordingly, we believe that these observations are widely applicable to obstetric patients in the United States at this time. The obstetric and fetal results are in accord with those reported at other centers and commonly assummed to be represenative of obstetric and fetal abnormalities that arise during the gestational episode.

The total group of 2,046 women was studied from the time of entry into the study and assessments *preceded* the development or recognition of various obstetric or fetal complications. This is the first time that serial multiple determinations of such laboratory values have been made in a large unselected group of women. This design allows exploration of the interrelationship between any particular nutrient in the blood and other hematologic values.

The various patterns of blood determinations that were carried out revealed many factors which may be explained in large part on the recognized hemodilutional effect which occurs during the gestational period. Thus, the decrease in mean hematologic values, serum protein, serum vitamins A and C might be attributed, in part at least, to this phenomenon. On the other hand, variations such as the increase in the mean levels of serum carotene and tocopherol, and urinary excretion of N^1-methylnicotinamide, cannot be related to the phenomenon of hemodilution. We accept these changes as normal physiologic occurrences of metabolic origin, the limits of which have been defined before making any effort to relate deviations from the pattern to obstetric or fetal complications.

The average nutrient intake of the women was below the recommended dietary allowances as set forth by the National Research Council. During the third trimester of pregnancy, there was a definite decrease in total caloric intake and an associated proportionate reduction in the consumption of most other nutrients.

In the total study group, not a single case of frank evidence of vitamin deficiency disease existed. The commonest physical stigma of nutritional significance was obesity, which was recorded in over 15 per cent of the women examined. In appraising the minor physical findings of debatable nutritional significance, the influence of age and parity, season, and trimester, have been assessed. The most pronounced influence determining the incidence of such physical signs has been identified as the variation between individual physician observers. When these influences are taken into account, the only physical

finding and nutrient level which can be related are gingivitis and ascorbic acid. The weakness of this relationship indicates that ascorbic acid lack was not the primary determining factor in the development of gingivitis. Obviously, the zone of nutriture of our sample is above that of clinically manifest deficiency disease.[16]

When obstetric and fetal abnormalities were related to measures of nutritional status (nutrient intakes, biochemical determinations, and physical signs) a variety of individual features were significantly different from the characteristics of the total group. In all findings, except the higher serum carotene levels of diabetic patients, the occurrence of statistically significant differences is a reflection of the large groups involved. The actual arithmetical differences in values are small and the averages compared are made up of overlapping individual values.

The positive findings in the data of the subgroups of obstetric and fetal complications as compared to the total group can be summarized as follows:

1. Pregnancy disease in general was associated with lowered calorie and nutrient intake, and elevated levels of total serum protein throughout pregnancy. Post partum, the serum vitamin A concentration was increased and there was an increase in the incidence of clinically detectable edema. These findings are consistent with a state of chronic illness.

2. In patients with rheumatic heart disease, the dietary intake was low. This was associated with the finding of either obesity or underweight. This subgroup contained no intermediate members with satisfactory weight rating. The implication for the low dietary intake seems obvious.

3. Among the diabetic patients the mean level of serum carotene was consistently high, and the serum level of vitamin C was elevated over that of the total group during the postpartum period. This first finding is characteristic of the diabetes; the second one is due to the lack of nursing of the infant.

4. The "anemia" developing during the puerperal or gestational period was hypochromic and could usually be related to complications associated with excessive blood loss. The group of patients who developed this anemia had low average intakes of iron and vitamin C, associated with generally low hematologic and other serum determinations. There was, as one might predict, an increased incidence of edema during the third trimester. The relative importance etiologically of nutrient intake and of blood loss, past and present, cannot be assigned. Good obstetric care demands attention to both of these points.

5. Among the pre-eclamptic and eclamptic patients there was a decreased nutrient intake, consistently so only for niacin. This was associated with a smaller than expected excretion of N^1-methylnicotinamide. *Prior to the recognition* of the toxemia, the group had, surprisingly, an elevation of the total serum protein. Physical examination of the pre-eclamptic patients indicated an increased incidence of obesity and edema, particularly during the third trimester and post partum. These findings do not support the widely held hypothesis that pre-eclampsia and eclampsia are due to protein deficiency. While it may be that

protein lack under other circumstances may be associated with these conditions, we cannot escape the interpretation that the residual pre-eclampsia and eclampsia which exist in the usual obstetrical population in the United States, such as we have described, are not related to a lack of protein. On this point our observations are in keeping with those of Scrimshaw,[17] Clement Smith,[18] and Williams and Fralin.[19] The obviously disturbed water balance and metabolic upsets in these patients, apparent in our series after the development of the toxemic states, result in changes in the serum protein concentrations which have led to the interpretation that toxemia is due to protein lack. Our study of the patient prior to the development of the manifest condition does not permit such an interpretation.

6. In those patients who developed puerperal complications or fever there was a decrease in the average level of serum vitamin A and hematologic values throughout gestation. The absolute magnitude of the differences in vitamin A was such as to question its physiologic significance.

7. Among the mothers of 72 infants who were stillborn or who died in the neonatal period, there was an increase in the average total serum protein and albumin, and an increase in the serum vitamin C during the postpartum period. Among the mothers of the stillborn infants there was an increased incidence of obesity. There was no suggestion of a deficiency component in these situations.

8. Among mothers of premature infants there was recorded a lower intake of ascorbic acid in association with a decreased level of this vitamin in the blood serum. Apart from the vitamin C the remainder of blood determinations showed slightly elevated values. On physical examination of this group there was an increased incidence of mothers judged to be "undernourished." These nutritional findings, plus the consideration of the interrelationship between prematurity and other obstetric complications, do not permit us to relate etiologically prematurity to maternal undernutrition.

9. Among 243 women who, for a variety of reasons, did not nurse their infants, the only significant deviation was an elevation of the serum vitamin C at postpartum examination. This is evidently a reflection of the absence of lactational drain in this group.

10. In those patients who had excessive degrees of blood loss at the time of delivery or in the puerperal period there was a significant postpartum decrease in hematologic values. This iron deficiency anemia was the obvious result of a complicated delivery.

11. In the mothers of the 22 sets of twins there was a decrease in the average hematologic and serum values evident in the third trimester. In addition, there was noted an increased incidence of edema among these patients.

We have explored the relationship between obstetric and fetal complications and the adequacy of nutrient intake. The only positive correlations found have been in the groups who had dietary intakes during the third trimester of less than 1,500 calories and less than 50 grams of protein. These were associated with an increased incidence of pregnancy disease and an increased finding of

pre-eclampsia and eclampsia. In both instances the abnormality appears to be responsible for the lowered intake, not vice versa.

Summary

1. The nutriture of 2,046 obstetric patients who attended the Vanderbilt University Hospital between 1945 and 1950 has been evaluated on the basis of nutrient intake, laboratory and biochemical determinations, and clinical physical examinations.

2. The metabolic and physiologic changes in these during the gestational period have been outlined.

3. Twenty-five abnormal obstetric and fetal conditions have been examined for evidence of nutritional stigmas during the gestational period.

4. Different levels of nutrient intake have been studied for any influence on the development of obstetric and fetal abnormalities.

5. In this group of patients who are reasonably representative of widespread obstetric experience in the United States, there is no clear indictment of nutritional lack as an important etiological agent in the numerous conditions studied.

6. The findings do direct attention to the effect of pregnancy and lactation upon the nutritional state of the woman, particularly during the postpartum period or when an obstetric complication occurs.

References

1. Darby, W. J., Densen, P. M., Cannon, R. O., Bridgforth, E. B., Martin, M. P., Kaser, M. M., Peterson, J. C., Christie, A., Frye, W. W., Justus, K., McClellan, G. S., Williams, C., Ogle, P. J., Hahn, P. F., Sheppard, C. W., Carothers, E. L., and Newbill, J. A.: J. Nutrition (in press).
2. Darby, W. J., McGanity, W. J., Martin, M. P., Bridgforth, E. B., Densen, P. M., Kaser, M. M., Ogle, P. J., Newbill, J. A., Stockell, A., Ferguson, M. E., Touster, O., McClellan, G. S., Williams, C., and Cannon, R. O.: J. Nutrition (in press).
3. McGanity, W. J., Cannon, R. O., Bridgforth, E. B., Martin, M. P., Densen, P. M., Newbill, J. A., McClellan, G. S., Christie, A., Peterson, J. C., and Darby, W. J.: Am. J. Obst. & Gynec. 67: 491, 1954.
4. Toverud, K. U., Stearns, G., and Macy, I. G.: Maternal Nutrition and Child Health, Bulletin of the National Res. Council, No. 123, Washington, D. C., 1950.
5. Food and Nutrition Board, National Research Council: Recommended Dietary Allowances, Revised 1948. National Res. Council Reprint & Circ. Series, No. 129, Washington, D. C., 1948.
6. Hahn, P. F., Carothers, E. L., Darby, W. J., Martin, M., Sheppard, C. W., Cannon, R. O., Beam, A. S., Densen, P. M., Peterson, J. C., and McClellan, G. S.: Am. J. Obst. & Gynec. 61: 477, 1951.
7. Boyd, E. M.: J. Clin. Investigation 13: 347, 1934.
8. Schrek, R.: Human Biol. 22: 65, 1950.
9. Ralli, E. P., Brandaleone, H., and Mandelbaum, T.: J. Lab. & Clin. Med. 20: 1266, 1935.
10. Dieckmann, W. J., and Wegner, C. R.: Arch. Int. Med. 53: 71, 1934.
11. Caton, W. L., Roby, C. C., Reid, D. E., and Gibson, J. G., II: Am. J. Obst. & Gynec. 57: 471, 1949.
12. Dieckmann, W. J.: Am. J. Obst. & Gynec. 32: 927, 1936.
13. Berlin, N. I., Hyde, G. M., Lawrence, J. H., Parsons, R. J., and Port, S.: Surg., Gynec. & Obst. 94: 21, 1952.
14. Garry, R. C., and Wood, H. O.: Nutrition Abstr. & Rev. 15: 591, 1945-1946.
15. Canadian Council on Nutrition: A Dietary Standard for Canada Approved by the Canadian Council on Nutrition, Ottawa, Dec. 7, 1948. Canadian Bulletin on Nutrition, Ottawa, 1950, vol. 2, no. 1.
16. Dann, W. J., and Darby, W. J.: Physiol. Rev. 25: 326, 1945.
17. Scrimshaw, N. S.: Am. J. Obst. & Gynec. 54: 428, 1947.
18. Smith, C. A.: J. Pediat. 30: 229, 1947.
19. Williams, P. F., and Fralin, F. G.: Am. J. Obst. & Gynec. 43: 1, 1942.

APPENDIX TABLE I. NUTRIENT FINDINGS, WOMEN WITH FACTORS COMPLICATING REPRODUCTIVE INTERLUDE, BY STAGE OF GESTATION, VANDERBILT COOPERATIVE STUDY

			MEANS								MEDIANS	
		NO. OF CASES	TOTAL CALORIES (CALORIES)	PROTEIN INTAKE (GM.)	ANIMAL PROTEIN (%)	CALCIUM (GM.)	IRON (MG.)	THIAMINE (MG.)	RIBO-FLAVIN (MG.)	NIACIN (MG.)	VITAMIN A INTAKE (I.U.)	VITAMIN C INTAKE (MG.)
TOTAL STUDY GROUP (2,046 CASES)	1ST TRIM.	277	2,130	75.0	65.9	1.07	13.4	1.48	2.49	12.1	6,650	66
	2ND TRIM.	1,206	2,180	75.3	65.0	1.07	13.7	1.49	2.50	12.0	6,550	62
	3RD TRIM.	1,634	2,010	69.8	64.9	0.99	12.6	1.39	2.29	10.9	5,850	54
			DEVIATIONS FROM MEANS OF TOTAL GROUP								MEDIANS[a]	
a. Pregnancy disease in general	1	30	−230*	−9.7*	−3.0	−.18*	−0.8	−.17	−.35*	−1.1	6,000	60
(212 cases)	2	130	−70	−2.4	−1.0	−.07	−0.1	+.01	−.09	−0.3	5,710	57*
	3	149	−80	−2.7	−0.7	−.03	−0.4	−.04	−.09	−0.8*	5,430	52
b. Chronic lung disease	1	3	+330	+13.3	+1.6	+.22	+3.6	+.47	+.76	+2.3	9,500	50
(23 cases)	2	11	+60	+0.6	−0.8	+.08	+0.2	+.12	+.12	−0.8	4,750	70
	3	14	−130	−4.1	−1.4	0	−0.6	−.17	−.15	−2.2*	5,500	53
c. Diffuse nontoxic goiter	1	1	−500	0	+11.6	+.58	−2.4	+.27	+.26	−3.1	7,500	90
(13 cases)	2	8	+70	+3.5	+0.6	+.12	+0.3	−.01	+.12	−0.5	5,250	67
	3	9	−100	−2.6	−0.8	+.11	+1.0	+.10	+.18	+0.5	8,500	83
d. Diabetes mellitus (7 cases)	1	2	−380	−10.0	+1.6	−.32	−0.4	−.48	−.74	−0.1	4,000	70
	2	3	−220	+3.0	+5.8	+.14	+2.0	+.16	+.75	+1.7	14,500	110
	3	5	−380	−6.8	−0.6	−.11	0	−.12	+.16	−0.3	7,500	70
e. Heart disease (11 cases)	1	2	−500	−20.0	−3.4	−.32	−4.4	−.18	−.98	−5.1	2,500	50
	2	6	−260	−7.0	−1.7	−.16	−1.4	−.29	−.50	−2.3	5,000	60
	3	7	−130	−4.8	−1.7	−.26	−3.1*	−.11	−.48	−0.8	2,830**	18**
f. Anemia, prenatal												
1st (3 cases)	1	2	+500	+10.0	−3.4	+.06	+0.6	+.12	+.02	+0.9	5,500	60
2nd (49 cases)	2	35	−80	−3.2	−1.7	−.08	−0.7	−.10	−.10	−0.5	5,900	53
3rd (193 cases)	3	156	−50	−1.5	+0.3	+.04	−0.6*	−.06	+.09	−0.6*	5,700	46**
g. Anemia, postpartum	1											
(<10 Gm. Hgb.)	2											
(23 cases)	3	18	−20	+1.3	+4.2	+.03	−0.9	−.04	−.10	−0.4	4,750	38

Level of probability for t and χ^2 tests for differences: *5%; **1%; ***0.1%.

[a] χ^2 –tests for vitamins A and C are based on proportions below 3,000 I.U./day and 20 mg./day, respectively.

APPENDIX TABLE I—CONT'D

		NO. OF CASES	MEANS: TOTAL CALORIES (CALORIES)	PROTEIN INTAKE (GM.)	ANIMAL PROTEIN (%)	CALCIUM (GM.)	IRON (MG.)	THIAMINE (MG.)	RIBOFLAVIN (MG.)	NIACIN (MG.)	MEDIANS: VITAMIN A INTAKE (I.U.)	VITAMIN C INTAKE (MG.)
h. Hyperemesis (15 cases)	1	6	−380	−13.3	+1.6	−.17	−2.8	−.28	−.48	−2.4	7,000	60
	2	12	−80	+1.4	+0.4	−.09	+1.0	+.01	0	+0.3	8,000	67
	3	13	−60	+0.6	+3.8	0	−0.4	+.11	−.12	−0.7	4,620	50
i. Pre-eclampsia and eclampsia (103 cases)	1	19	−230	−11.1*	−4.2*	−.13	−1.9*	−.22	−.42*	−2.8**	5,500	59
	2	69	−90	−3.1	−0.6	−.03	−0.8	−.08	−.12	−1.1*	5,460	56*
	3	77	−220***	−4.3	+0.7	−.05	−0.7	−.09	−.10	−1.1*	5,310	47
j. Placenta previa (7 cases)	1	0	—	—	—	—	—	—	—	—	—	—
	2	2	−180	−5.3	+2.4	+.18	+0.3	+.26	+.25	−1.0	8,500	120
	3	3	−50	−1.5	+6.0	−.11	−1.0	+.27	−.04	+0.7	6,500	65
k. Premature separation of placenta (24 cases)	1	6	−420	−13.3	+0.8	−.15	−3.1*	−.28	−.40	−1.7	4,500	50
	2	17	−30	+0.3	+3.9	+.05	−0.5	+.06	+.13	−0.2	5,875	63
	3	14	−260	−4.8	+3.6	0	−0.9	−.09	−.08	−0.9	7,000	51
l. Weeks' gestation <38 weeks (234 cases)	1	31	−150	−5.2		−.14	−0.8	−.02	−.24	−0.4	6,500	67
	2	132	−20	−0.3	−0.1	+.02	+0.2	0	+.01	0	7,000	64
	3	124	−70	−1.9	−0.7	−.04	−0.1	−.03	−.06	−0.1	6,270	56
m. Duration of labor ≥20 hr. (227 cases)	1	35	0	−0.3	−0.4							
	2	145	+10	+1.8	+0.5							
	3	196	−30	−0.3	+1.0							
n. Delivery complications (109 cases)	1	15	−170	−8.0	−3.8							
	2	62	+110	+2.4	−2.7*							
	3	84	+20	+1.5	−0.4							
o. Cesarean section (65 cases)	1	12	+60	+0.8	+2.8	+.06	−0.1	−.03	−.07	+0.4	9,000	74
	2	38	−150	−3.2	+2.8	−.01	−0.4	+.01	−.02	−0.4	7,000	60
	3	43	−120	−3.2	+1.6	−.01	−0.4	−.02	−.07	−0.7	6,040	54
p. Labor complications (not j or k) (123 cases)	1	17	+70	+1.2	−2.2	−.02	+1.4	−.02	−.12	+0.6	6,500	68
	2	72	−90	−0.6	+0.6	+.02	+0.1	+.02	−.05	−0.1	7,000	68
	3	93	−100	−3.0	−0.2	−.06	−0.2	−.06	−.10	−0.2	6,500	56
q. Postpartum hemorrhage (21 cases)	1	3	−170	−3.3	−3.4	+.14	−1.1	−.23	−.07	−1.1	6,500	110
	2	14	−60	+3.3	+1.0	+.02	+0.4	+.09	+.14	−0.1	6,000	67
	3	18	+50	+3.5	+3.2	+.12	−0.1	+.03	+.26	+1.1	6,330	55

r. Abortions	1	3	0	+3.3	+5.0	+.22	+0.2	−.13	+.43	−0.4	4,500	50
(20 cases)	2	4	+190	+9.7	−2.6	+.36	+1.3	+.26	+.75	+1.0	11,000	80
	3	0	—	—	—	—	—	—	—	—	—	—
s. Prematurity	1	12	0	+3.3	+1.2	0	−0.4	+.19	−.02	+0.6	5,500	53
(115 cases)	2	61	−40	+0.5	+1.0	+.02	0	0	−.01	−0.5	6,280	62*
	3	59	−80	−0.9	+0.8	−.03	0	+.08	−.01	−0.2	5,250	48***
t. Twins	1	2	−260	−10.0	−5.9	−.07	+0.6	−.03	−.24	−2.1	12,500	90
(22 cases)	2	12	+70	+3.9	−2.2	−.03	+0.5	−.21	−.08	−1.3	6,000	64
	3	16	−150	−1.7	−1.8	−.08	+0.2	+.16	−.17	+0.7	4,330	45
u. Congenital malformations	1	6	+200	+5.8	−0.5	+.08	+1.7	−.03	+.18	+0.6	8,000	80
(55 cases)	2	33	+40	+0.1	−1.0	−.06	+0.4	+.04	−.02	−0.5	6,330	67
	3	42	−90	−3.6	−1.4	−.10	−0.3	−.02	−.16	−0.1	5,330	55
v. Stillbirths and neonatal deaths	1	8	−160	−5.0	−2.2	−.17	−1.2	−.03	−.36	−1.1	4,000	60
(71 cases)	2	45	+10	+1.0	+1.4	+.01	+0.1	+.02	+.10	−0.2	6,860	70
	3	34	−150	−3.9	+5.1**	−.02	−1.2	−.09	−.08	−0.6	6,000	57
w. Puerperal complications	1	34	0	+0.3	+1.8	−.01	−0.1	+.01	+.09	+0.2	6,290	63
(265 cases)	2	157	−30	−0.8	+0.4	−.01	−0.3	+.02	−.01	−0.1	6,300	56
	3	210	+40	+1.4	+1.4*	+.04	−0.2	+.04	+.06	+0.3	5,800	55
x. Puerperal fever	1	15	+30	+2.0	+1.0	−.08	+0.4	+.09	0	+0.9	5,500	62
(110 cases)	2	61	+10	+0.7	+0.3	0	+0.4	+.14*	−.02	+0.2	6,560	61*
	3	89	+90	+3.3	+0.5	+.06	+0.2	+.08	+.08	+0.6	5,750	55
y. Mothers did not nurse	1	27	+50	+1.8	+0.5	+.02	+0.7	+.16	+.06	+1.1	7,620	73
(243 cases)	2	128	+20	+1.2	+0.7	+.02	0	+.05	+.03	+0.1	6,860	64
	3	173	−40	−1.2	+1.2	−.04	−0.3	−.02	−.06	−0.1	5,430	53

APPENDIX TABLE II. LABORATORY FINDINGS, WOMEN WITH FACTORS COMPLICATING REPRODUCTIVE INTERLUDE, BY STAGE OF GESTATION, VANDERBILT COOPERATIVE STUDY

			MEAN VALUES								MEDIANS			
		NO. OF CASES	HEMOGLOBIN (GM./100 ML.)	PCV (%)	MCV (CUBIC MICRONS)	MCHC (%)	TSP (GM./100 ML.)	SERUM ALBUMIN (GM./100 ML.)	SERUM VIT. A (I.U./100 ML.)	SERUM CAROTENE (μG/100 ML.)	SERUM VIT. C (MG./100 ML.)	THIAMINE EXCRETION (MG./2 HR.)	RIBOFLAVIN EXCRETION (MG./2 HR.)	N^1-METHYLNICOTINAMIDE EXCRETION (MG./2 HR.)
TOTAL STUDY GROUP (2,046 CASES)	1st trim.	343	13.02	38.7	90.3	33.61	6.89	4.55	111	117	.47	.134	.86	6.6
	2nd trim.	1376	12.22	36.4	89.7	33.55	6.54	4.24	112	145	.47	.115	.85	7.9
	3rd trim.	1974	11.66	35.3	89.5	32.96	6.34	4.04	100	160	.35	.089	.72	9.6
	Postpartum	1555	12.98	40.3	89.0	32.25	7.14	4.67	140	120	.20	.100	.61	5.2
			DEVIATIONS FROM MEANS OF TOTAL GROUP								MEDIANS[a]			
a. Pregnancy disease in general (212 cases)	1	45	− .19	− .8	+ .8	+ .16	+.10	−.09	0	− 6	.34*	.140	.86	5.8
	2	145	− .12	− .1	− .8	− .18	+.04	+.02	+ 2	+ 3	.43	.110	.73	7.4
	3	195	− .07	0	− .4	− .10	+.10***	+.04	+ 1	− 3	.33	.080	.63*	8.8
	PP	154	− .13	− .4	+ .3	− .02	+.02	−.09**	+ 6*	+ 5	.23	.092	.56	5.0
b. Chronic lung disease (23 cases)	1	4	+ .43	+ .4	− .8	− .12	+.21	+.30	−16	− 17	.40	.120	.90	5.0
	2	13	+ .08	− .4	−1.2	− .12	−.04	+.26*	+10	− 9	.30	.090	.60	5.5
	3	20	− .21	+ .1	−1.0	− .36	+.15	+.01	+ 2	+ 2	.37	.065	.75	8.8
	PP	12	− .36	−1.1	+ .1	− .10	−.22	−.04	− 5	+ 13	.17	.080	.50	3.3
c. Diffuse nontoxic goiter (13 cases)	1	2	− .57	−4.0	−3.2	+1.88	+.21	+.10	−21	+ 3	.50	.210	1.50	7.5
	2	9	+ .12	+ .4	+2.3	+ .08	−.05	−.02	− 9	− 2	.35	.127	.75	10.3
	3	12	+ .04	+ .9	+ .8	− .80	+.08	+.12	0	+ 26	.40	.150	.98	15.0
	PP	8	− .03	+ .1	+3.0	0	−.20	−.09	+ 2	0	.35*	.120	.60	4.4
d. Diabetes mellitus (7 cases)	1	2	+ .43	+2.2	+1.8	− .12	−.09	−.20	− 1	+ 43	.80	.240	1.65	5.0
	2	5	+ .43	+ .6	− .7	+ .56	−.13	−.13	−14	+ 66**	.70	.150	.68	6.2
	3	6	+ .62	+1.1	+ .8	+ .54	+.10	−.04	+16	+ 86***	.55	.150	.82	11.9
	PP	6	+ .64	+ .8	+ .5	+ .58	+.22	+.03	+25	+113***	.80*	.240	.70	4.2
e. Heart disease (11 cases)	1	2	− .57	− .2	−10.8	− .12	+.36	−.35	− 1	− 17	.40	.120	1.20	5.0
	2	9	+ .01	− .2	− .5	+ .08	+.15	−.02	− 9	− 24	.30	.083	.52	6.2
	3	8	− .09	0	− .6	− .22	−.11	−.10	− 5	+ 4	.28	.060	.50	7.5
	PP	10	− .13	−1.0	0	+ .64	+.20	+.01	− 5	− 29	.18	.083	.82	4.7

f. Anemia, on any occasion (<10 Gm. Hgb.) (232 cases)	1	39	−1.11***	−2.5***	−4.0**	− .82**	+.04	−.10	− 2	0	.30*	.120	.85	6.4
	2	171	−1.40***	−3.0***	−3.6***	−1.46***	+.01	−.08**	− 8**	+ 4	.44	.110	.85	8.6
	3	219	−2.27***	−4.3***	−5.9***	−2.22***	−.06*	−.08**	− 7*	− 3	.29**	.078	.67	9.3
	PP	173	−1.29***	−2.5***	−3.4***	−1.20***	+.01	−.03	− 5*	− 4	.20	.091*	.60	4.9*
g. Anemia, post partum (<10 Gm. Hgb.) (23 cases)	1	3	− .90	−2.8	+ .1	+ .22	+.16	+.07	−15	+ 23	.30	.105	.52	6.9
	2	17	− .59*	−1.0	−3.6	− .92*	+.13	+.18	−10	+ 4	.46	.108	.80	10.0
	3	18	−1.21***	−2.0*	−4.8*	−1.80***	+.14	−.03	+ 1	+ 6	.20	.069	.85	13.1
	PP	23	−4.01***	−8.8***	−7.0***	−3.06***	−.18	−.13	−18*	+ 6	.19	.065	.58	5.9
h. Hyperemesis (15 cases)	1	6	+ .26	+1.4	+4.2	− .46	+.01	−.20	+19	− 17	.40	.090	.90	4.5
	2	13	+ .15	+ .7	−2.0	− .12	+.14	+.17	+16*	− 9	.36	.114	.69	8.0
	3	15	− .48	−1.1	−1.1	− .18	−.15	−.11	+14	+ 25	.50	.084	.78	10.5
	PP	14	+ .54	+ .6	+1.2	+ .38	+.06	+.02	+10	− 3	.36	.078	.66	6.0
i. Pre-eclampsia and eclampsia (103 cases)	1	19	+ .33	+ .6	−3.2	+ .24	+.06	0	+ 1	− 4	.36	.125	.51	4.9*
	2	73	+ .07	+ .6	−1.2	− .10	+.14**	+.10*	+ 2	− 6	.39	.123	.76*	6.8
	3	94	− .10	0	−2.6**	− .42*	+.05	+.04	+ 4	− 2	.30	.080	.57	9.4
	PP	75	− .22	− .6	+ .4	+ .02	+.04	−.02	+ 6	+ 10	.18	.082	.57	4.7**
j. Placenta previa (7 cases)	1	0	—	—	—	—	—	—	—	—	—	—	—	—
	2	2	+ .73	+ .8	+2.3	+ .96	−.19	+.11	−36	− 26	.30	.150	1.20	16.2
	3	7	+ .22	0	−6.8*	+1.26	+.06	+.11	−10	− 20	.30	.045	.60	12.5
	PP	4	−1.78**	−4.2**	−3.2	−1.76*	−.20	+.21	+ 2	− 20	.13	.255	.45	6.9
k. Premature separation of placenta (24 cases)	1	5	− .17	+ .2	−3.2	− .32	+.18	−.08	−25	− 33	.45	.105	.75	6.2
	2	21	− .29	− .4	+ .8	− .56	+.21*	+.11	− 3	− 10	.38	.126	1.26	7.2
	3	19	+ .16	− .3	−2.8	−.02	+.13	+.05	0	− 22	.22	.070	.47	10.6
	PP	24	− .78**	−2.3***	−1.0	−.10	−.01	−.14	0	− 1	.23	.085	.58	6.2
l. Weeks' gestation <38 weeks (234 cases)	1	34	+ .02	+ .6			−.03	−.06	− 1	+ 8	.35	.137	.79	7.8
	2	158	− .04	0	+ .1	− .04	−.01	+.02	− 3	− 2	.39	.113	.90	8.6
	3	198	+ .06	+ .3	− .2	− .20	+.03	−.01	+ 2	− 4	.33	.077	.63	10.1
	PP	182	+ .03	0	+1.5*	+ .06	−.01	+.01	− 2	− 2	.20	.098	.58	4.9
m. Duration of labor ≥20 hr. (227 cases)	1	40	+ .23	+ .4	+ .6	+ .28								
	2	156	+ .17	+ .1	−1.0	+ .24								
	3	219	+ .08	+ .2	+ .5	− .04								
	PP	172	− .11	− .2	− .7	− .12								

Level of probability for t and χ^2 tests for differences: *5%; **1%; ***0.1%.

*χ^2 – tests for serum vitamin C are based on proportions below 0.2 mg./100 ml.; for urinary thiamine, 0.06 mg./2 hr.; for urinary riboflavin, 0.3 mg./2 hr.; and for urinary N^1-methylnicotinamide, 5.0 mg./2 hr. during pregnancy and 2.5 mg./2 hr. post partum.

APPENDIX TABLE II—CONT'D

			MEAN VALUES								MEDIANS			
		NO. OF CASES	HEMOGLOBIN (GM./100 ML.)	PCV (%)	MCV (CUBIC MICRONS)	MCHC (%)	TSP (GM./100 ML.)	SERUM ALBUMIN (GM./100 ML.)	SERUM VIT. A (I.U./100 ML.)	SERUM CAROTENE (μG/100 ML.)	SERUM VIT. C (MG./100 ML.)	THIAMINE EXCRETION (MG./2 HR.)	RIBOFLAVIN EXCRETION (MG./2 HR.)	N^1-METHYLNICOTINAMIDE EXCRETION (MG./2 HR.)
n. Delivery complications (109 cases)	1	21	− .28	− .5	+2.7	+ .02								
	2	73	+ .02	+ .1	− .3	− .28								
	3	102	+ .03	+ .1	− .4	− .22								
	PP	79	− .05	+ .2	+ .2	− .06								
o. Cesarean section (65 cases)	1	16	+ .24	+ .8	−2.3	+ .12	+.06	+.10	− 5	+ 21	.60	.132	1.32	6.5
	2	42	+ .13	− .1	+ .6	− .38	−.02	−.01	+ 5	+ 8	.55	.112	.72	7.3
	3	57	− .05	− .1	− .2	+ .14	+.07	+.03	+ 2	+ 11	.39	.076	.87	10.7
	PP	49	− .31	− .6	+ .4	− .42	+.03	−.04	+ 4	+ 11	.32*	.108	.73	4.9
p. Labor complications (not j or k) (123 cases)	1	19	+ .06	+ .4	+ .7	− .06	−.14	−.02	− 4	− 2	.52	.108	1.28	5.8
	2	81	− .03	− .4	+1.6	+ .12	+.05	+.01	+ 2	+ 3	.41	.114	.81	6.7
	3	113	0	+ .2	+2.0*	− .04	+.07	+.01	+ 3	+ 10	.34	.080	.92	8.5
	PP	94	+ .10	− .2	+ .7	+ .30	+.05	−.06	− 4	+ 7	.26	.092	.68	5.3
q. Postpartum hemorrhage (21 cases)	1	3	− .90	−1.9	−8.2	+ .88	+.16	−.20	− 8	− 4	1.10	.270	1.05	4.4
	2	15	+ .50	+1.4	+ .3	+ .16	+.17	+.11	+ 2	− 14	.48	.078*	1.23	6.6
	3	21	+ .12	+ .3	0	− .18	+.09	+.02	− 1	− 4	.38	.070	.75	8.8
	PP	17	− .82**	−1.9*	− .2	− .70	+.12	−.08	− 4	− 10	.32	.110	.70	5.6
r. Abortions in hospital (20 cases)	1	10	− .47	+ .2	+2.2	−1.12	+.21	+.07	− 5	+ 11	.47	.096	.80	4.4
	2	10	− .67	+ .3	−1.7	−1.44*	+.15	−.05	− 4	− 14	.67	.150	.75	7.5
	3	0	—	—	—	—	—	—	—	—	—	—	—	—
	PP	15	+ .14	− .9	−3.6	+1.30**	+.13	+.22*	+ 4	+ 4	.50*	.087	.64	4.8

s. Prematurity	1	16	+ .18	+1.3	+3.0	− .62	+.08	+.08	+ 4	+ 4	.47	.120	.75	6.5
(115 cases)	2	78	+ .09	+ .1	+ .2	+ .14	+.04	+.01	+ 3	− 6	.37*	.110	1.07	7.3
	3	95	+ .34*	+ .8*	− .1	+ .12	+.02	+.01	+ 9**	− 8	.26*	.083	.81	8.2
	PP	88	+ .40**	+ .9**	+2.8**	+ .38*	−.03	−.08	+ 3	− 6	.29	.082*	.52	5.0
t. Twins	1	3	+ .10	+1.4	+6.8	− .46	+.26	−.10	− 8	− 17	.65	.075	.75	5.6
(22 cases)	2	13	− .54	−1.0	− .8	− .42	−.12	−.05	−13	+ 19	.19*	.135	1.42	8.4
	3	21	− .64*	−1.6*	−5.9**	− .74	−.13	−.17*	−18**	− 12	.17*	.085	.82	8.8
	PP	19	− .06	+ .8	− .2	− .40	+.01	+.07	+ 8	− 4	.16	.103	.45	4.7
u. Congenital malformations	1	14	+ .50	+ .1	+3.2	+ .88	+.01	−.05	− 9	− 2	.50	.195	1.20	6.6
	2	36	+ .08	+ .1	− .1	+ .30	−.01	+.08	− 2	+ 8	.45	.118	.88	8.9
(55 cases)	3	50	0	− .1	0	0	−.01	+.04	− 1	+ 5	.35	.092	.72	8.2*
	PP	44	+ .14	− .1	+ .6	+ .28	+.03	+.04	+ 1	+ 4	.20	.115*	.68	5.9
v. Stillbirths and neonatal deaths	1	9	+ .32	+1.2	−3.2	− .24	+.06	+.25	− 6	− 17	.45	.150	.75	6.8
	2	55	+ .05	+ .2	+ .2	− .10	+.11	+.13*	+ 6	− 2	.45	.117	.80	8.5
(71 cases)	3	51	+ .20	+ .2	+ .2	+ .10	+.16**	+.04	+ 4	− 3	.34	.095	.58	9.2
	PP	60	− .05	− .6	+1.1	+ .14	−.04	−.04	+ 5	+ 16*	.33*	.086	.51	5.8
w. Puerperal complications	1	39	+ .12	− .3	− .3	+ .68*	+.04	+.02	− 1	− 1	.49	.136	.94	6.1
	2	174	− .05	− .2	−1.4**	+ .02	+.01	+.02	− 6***	− 2	.52	.116	.94	7.1*
(265 cases)	3	254	− .24**	− .3	+ .4	− .30***	0	−.01	− 6***	− 6	.35	.082	.70	8.9
	PP	183	− .25**	− .6	−1.0	− .06	−.04	−.02	−10***	− 4	.20	.090	.65	4.8
x. Puerperal morbidity	1	18	+ .04	+ .3	+ .6	+ .22	+.09	+.02	− 4	+ 1	.49	.130	.75	6.4
	2	70	+ .11	+ .2	−1.8*	+ .16	+.02	+.02	− 5	+ 2	.51	.110	.84	6.9
(110 cases)	3	107	− .27*	0	− .2	− .42*	+.06	0	− 6*	− 7	.33	.081	.62	8.5
	PP	73	− .26	− .7	−1.8	+ .08	−.02	−.04	−13**	− 3	.24	.094	.63	4.8
y. Mothers did not nurse	1	33	− .09	+ .1	−1.4	− .20	+.02	−.01	+ 3	− 6	.48	.141	.81	6.5
	2	146	+ .11	0	− .3	+ .24	+.02	+.02	+ 2	+ 1	.43	.108	.87	7.7
(243 cases)	3	226	+ .19*	+ .5	− .1	+ .04	+.09***	+.03	+ 5*	− 4	.32	.082	.64	8.9
	PP	180	− .02	− .1	+ .9	+ .02	−.05	−.07*	0	+ 4	.32***	.089*	.54	5.5

PLACENTAL GLOBULIN SKIN SENSITIVITY, WITH SPECIAL REFERENCE TO TOXEMIAS OF PREGNANCY

BERNARD LAPAN, M.D., AND IRVING ALFRED SHEY, M.D., NEW YORK, N. Y.

(From the Departments of Obstetrics and Gynecology, Lebanon and Morrisania City Hospitals, New York)

THE placenta probably plays an important role in the etiology of the eclamptogenic toxemias of pregnancy. The literature on this subject has been reviewed by Page[1] and by Dieckmann.[2] It has been assumed that the placenta, through anoxemia or infarction, releases some toxic materials into the maternal organism, and that its elaboration of hormones and enzymes and its permeability undergo alterations which may play a part in the development of pre-eclampsia and eclampsia. Hunt and his associates[3] in a survey of the subject of placental infarction and eclampsia concluded that the degenerated placenta liberates autolysates which give rise to toxemia in the mother in proportion to the degree in which they are absorbed, and the rapidity in which they can be excreted by the mother.

Several of these autolysates or toxic substances have been implicated in the pathogenesis of pre-eclampsia and eclampsia. According to the extensive experimental work of Schneider,[4] one of these substances is thromboplastin. The Smiths and their co-workers[5] believe that a toxic euglobulin is an etiological factor and that it can be neutralized by penicillin.

Some immunologic mechanisms involving placental, fetal, or other protein as a factor in pre-eclamptic toxemia have been demonstrated or postulated by such investigators as Yamada,[6] Junghans,[7] and Jegorov.[8, a, b] According to Urbach and Gottlieb,[9] placental protein is foreign to the pregnant woman. This is denied by Kaku and his associates,[10a, 10b] who have recently demonstrated immunologic and allergic reactions to placental polysaccharides in toxemia. Kaku believes that the placental proteins cannot be isoantigenic, and that the antigenic factor is in the polysaccharide fractions. Youssef and Barsoum[11] have revived an old theory that an allergy to pregnancy is a cause of hyperemesis gravidarum.

Lin[12] produced toxemia experimentally in rats by sensitizing them to placental extract before pregnancy, thus demonstrating an allergic mechanism. Attempts have been made by Hoffman[13] at treating toxemias of pregnancy with antihistaminic drugs without conclusive results.

This study was undertaken to determine whether or not there is cutaneous sensitivity in pregnant and nonpregnant women to the placental proteins of pre-eclampsia. Previous studies of one of us[14] had indicated that the antigenic substances with which we are concerned could be found mainly in the globulin fraction of placental extracts.

Materials and Methods

Intradermal tests were done by the standard technique, using not more than 0.05 c.c. of fluid. Control injections were always made, using plain diluent. Results were recorded in 15 minutes and the areas of reaction were measured in millimeters. Any pseudopodia surrounding the wheals were noted. We considered positive only those tests in which the antigen gave at least 0.5 cm. greater reaction than the control. Over 800 intracutaneous tests were performed in 189 patients in the course of this study.

Placental toxemic globulin was extracted from the placenta in a case of typical severe pre-eclampsia, which was frozen immediately after delivery and taken to the laboratory for extraction. The frozen placenta was thawed and decapsulated, and 200 grams of tissue homogenized in a Waring blender with 200 c.c. of 0.9 per cent sodium chloride and allowed to stand two hours. The material was filtered, yielding 200 c.c. of filtrate. This was treated with an equal volume of saturated ammonium sulfate and allowed to stand overnight, flocculating the globulin fraction. The globulin was collected by centrifugation, redissolved in 0.9 per cent sodium chloride, placed in a cellophane sac, and dialized against running tap water for two days, causing the globulin to precipitate.

The precipitated globulin was redissolved in 100 c.c. of 0.9 per cent saline, and Merthiolate was added to 1:10,000 concentration. The solution was rendered sterile by Berkefeld filtration. Sterility tests were run on the final containers, and the product produced no observable symptoms when 4.0 c.c. was injected into each of two 450 gram guinea pigs and 0.5 c.c. into each of two 20 gram mice. This final solution was called 1:100, according to convention in describing allergens. However, 1 c.c. of final solution represented the globulin in 1 gram of placenta, and contained 0.4 mg. protein nitrogen and 2.5 mg. protein per cubic centimeter.

A random vial of commercially available immune globulin (Lederle), which is made from pooled placentas and which contained 160 mg. of protein nitrogen per cubic centimeter was diluted 1:50 so that the final test solution contained 3.2 mg. of protein nitrogen per cubic centimeter. This substance was chosen as a control because it is a widely known placental globulin and highly standardized as a commercial biologic product.

Additional tests were made using whole protein extract of a normal placenta delivered by cesarean section. The extraction was performed by precipitating the placental proteins with acetone to 90 per cent concentration. The final solution contained 0.15 mg. nitrogen in 1 c.c. However, because the method of extraction was different from that of the toxemic globulin, and because the number of cases tested was limited, the results were not included in this report.

The patients who received the intradermal tests belonged to the following categories:

I. Toxemic cases (Tables I, II, X, XI)
   - A. Pre-eclampsia and eclampsia
   - B. Essential hypertension with superimposed pre-eclampsia
   - C. Essential hypertension, uncomplicated
   - D. Chronic nephritis or low-reserve kidney

II. Controls (Tables III-IX)
   - A. Antepartum clinic patients
   - B. Postpartum hospital patients
   - C. Males
   - D. Nulligravid gynecologic patients
   - E. Early pregnancies, terminated (abortions or ectopic pregnancies)

TABLE I. SUMMARY OF SKIN REACTIONS TO TOXEMIC AND IMMUNE GLOBULINS

	TOXEMIC GLOBULIN		IMMUNE GLOBULIN	
	NUMBER OF CASES	PER CENT POSITIVE	NUMBER OF CASES	PER CENT POSITIVE
Nonpregnant gravidas (Table III)	8	88	8	37
Nulligravidas (Table IV)	18	67	18	33
Males (Table V)	5	40	5	0
Early abortions and ectopic pregnancies (Table VI)	22	48	22	28
Ante partum:				
Primiparas (Table VII)	21	28	0	
Multiparas (Table VIII)	34	30	0	
Post partum (Table IX)	25	20	25	4
Toxemias: (Table X)				
Pre-eclampsia and eclampsia	35	83	14	7
Essential hypertension with superimposed pre-eclampsia	3	66	1	0
Essential hypertension, uncomplicated	11	27	4	0
Chronic nephritis	5	80	0	

TABLE II. REACTIONS OF NORMAL AND TOXEMIC WOMEN TO TOXEMIC GLOBULIN IN THE THIRD TRIMESTER OF PREGNANCY

	NORMAL CASES		TOXEMIC CASES	
	NUMBER OF PATIENTS TESTED	PER CENT POSITIVE	NUMBER OF PATIENTS TESTED	PER CENT POSITIVE
7 months	14	22	10	70
8 months	7	29	11	82
9 months	20	45	13	81

TABLE III. NONPREGNANT CONTROLS: GRAVIDAS

INITIALS	AGE	RACE	GRAVIDA	PARA	DIAGNOSIS	OTHER ALLERGY	PREVIOUS TOXEMIA	TOXIC GLOBULIN	IMMUNE GLOBULIN	REMARKS
W. W.	39	N	i	0	Endometrial polyp	0	0	1+	1+	
								1+	0	
M. D.	57	W	ii	0	Postmenopausal bleeding	0	0	3+	2+	
								4+	1+	
I. C.	28	N	i	0	Salpingitis	+	0	2+	1+	Temp. 104° F.
								2+	0	Temp. normal
								1+	0	Temp. normal
R. B.	40	W	ii	0	Fibroids	0	0	3+	0	
								4+	0	
P. P.	51	N	i	i	Menorrhagia	0	0	3+	1+	
								3+	0	
								3+	1+	
M. S.	30	N	iv	iv	Gartners' cyst	0	0	4+	2+	
								4+	2+	
R. T.	62	N	iv	iii	Cystorectocele	0	0	0	0	
								1+	1+	
								0	0	
P. M.	77	W	v	iii	Carcinoma of ovary	0	0	3+	0	
								4+	0	
					Per cent positive			88	37	

The patients with toxemia were selected according to the criteria of the American Committee on Maternal Welfare. Doubtful cases were not included. The patients with uncomplicated essential hypertension were included for comparison. Whenever possible, the skin tests were repeated after an in-

TABLE IV. NONPREGNANT CONTROLS: NULLIGRAVIDAS

INITIALS	AGE	RACE	GRAVIDA	PARA	DIAGNOSIS	OTHER ALLERGY	PREVIOUS TOXEMIA	SKIN TESTS: TOXIC GLOBULIN	SKIN TESTS: IMMUNE GLOBULIN	REMARKS
S. B.	39	N	0	0	Fibroids	0	0	3+	0	
								3+	0	
								2+	0	
								2+	0	
L. G.	39	N	0	0	Functional bleeding	+	0	2+	0	
								1+	0	
A. C.	46	N	0	0	Fibroids	0	0	4+	1+	
								4+	0	
M. H.	24	N	0	0	Ovarian cyst. Salpingitis	0	0	0	0	
								0	0	
P. B.	25	W	0	0	Bartholin's cyst	0	0	2+	0	
								3+	0	
G. A.	23	N	0	0	Fibroids	0	0	2+	0	
								1+	0	
M. S.	27	N	0	0	Fibroids	0	0	0	2+	
								0	1+	
A. C.	39	W	0	0	Carcinoma of cervix	+	0	2+	2+	Before radiation
								3+	1+	After radiation
C. B.	39	N	0	0	Fibroids	0	0	4+	0	
								3+	0	
								3+	0	
B. T.	26	N	0	0	Drug addict	+	0	3+	0	
								3+	0	
J. R.	20	N	0	0	Salpingitis	0	0	0	0	
L. B.	15	W	0	0	Anovulatory bleeding	0	0	0	0	Before transfusion
								0	0	After transfusion
								0	0	After transfusion
F. D.	33	N	0	0	Fibroids	0	0	3+	0	
								2+	0	
M. S.	21	W	0	0	Appendicitis	0	0	2+	0	
								3+	2+	
A. R.	31	N	0	0	Cervical polyp	0	0	4+	0	
								2+	0	
M. E.	19	N	0	0	Salpingitis	+	0	0	1+	
								0	2+	
R. S.	35	W	0	0	Functional bleeding	0	0	2+	0	
								2+	2+	
R. J.	18	W	0	0	Salpingitis	0	0	0	2+	
								0	1+	
					Per cent positive			67	33	

TABLE V. CONTROLS: MALES

INITIALS	OTHER ALLERGY	SKIN REACTIONS: TOXIC GLOBULIN	SKIN REACTIONS: IMMUNE GLOBULIN
I. S.	+	3+	0
J. B.	0	0	0
B. S.	0	2+	0
C. W.	+	0	0
J. M.	0	0	0
Per cent positive		40	0

TABLE VI. CONTROLS: ECTOPIC PREGNANCIES AND ABORTIONS

INITIALS	AGE	RACE	GRAVIDA	PARA	DIAGNOSIS	OTHER ALLERGY	PREVIOUS TOXEMIA	SKIN TESTS: TOXIC GLOBULIN	SKIN TESTS: IMMUNE GLOBULIN	REMARKS
A. B.	23	N	i	0	Incomplete abortion	0	0	0	1+	
C. G.	25	N	ii	0	Incomplete abortion	0	0	0	0	Before transfusion
								0	2+	After transfusion
E. M.	35	W	i	0	Incomplete abortion	0	0	3+	0	After transfusion
								2+	0	After transfusion
D. D.	20	W	i	0	Incomplete abortion	0	0	2+	0	
								3+	0	
L. C.	18	N	i	0	Incomplete abortion	0	0	3+	0	
								4+	1+	
A. W.	41	W	i	0	Incomplete abortion	0	0	3+	1+	After transfusion
								3+	0	After transfusion
L. W.	20	N	i	0	Ectopic	0	0	0	0	
								0	0	
								0	0	
B. J.	26	N	ii	0	Ectopic	0	0	0	0	
								0	0	
T. N.	22	N	i	0	Ectopic	0	0	0	0	
								0	0	
J. J.	21	N	iii	ii	Incomplete abortion	0	0	0	0	
E. T.	25	N	i	0	Ectopic	0	0	2+	1+	
								0	1+	
E. T.	25	N	ii	i	Incomplete abortion	0	+	0	0	
								0	0	
S. S.	31	N	i	0	Ectopic	0	0	3+	0	
								2+	0	
P. H.	22	W	i	0	Incomplete abortion	0	0	0	0	
								0	0	
M. Q.	40	N	iv	iii	Incomplete abortion	0	+	0	1+	5 months pregnant
								0	1+	
C. D.	27	W	vi	iii	Incomplete abortion	0	0	2+	0	Fever
								2+	0	Fever
M. H.	34	N	iv	ii	Incomplete abortion	+	0	1+	0	
								1+	0	
H. G.	21	W	i	0	Incomplete abortion	0	0	4+	1+	Fever
								1+	1+	Fever
D. S.	30	N	i	0	Ectopic	0	0	0	2+	After transfusion
								0	2+	After transfusion
H. F.	24	W	i	0	Incomplete abortion	+	0	3+	0	
								3+	2+	
L. B.	39	N	ii	i	Ectopic	0	0	0	1+	
								0	0	
R. D.	21	W	i	0	Incomplete abortion	0	0	0	0	
								0	0	
G. W.	17	W	i	0	Complete abortion	0	0	2+	0	
								1+	0	
A. F.	25	W	i	0	Incomplete abortion	0	0	0	0	
								0	0	
R. D.	23	N	ii	0	Ovarian cyst. Uterine pregnancy	0	0	2+	4+	
								0	0	
								0	1+	
						Per cent positive		48	28	

terval of from two to five days. Many of our patients were retested up to four times, at intervals of two days or more. The positive reactions to the skin tests were all immediate. There were no observed delayed reactions, i.e., 24 hours or more after the intracutaneous injection, such as seen in tuberculin tests. No attempts were made to determine the maximum dilutions of antigens at which the tests remained positive.

TABLE VII. CONTROLS: ANTEPARTUM PRIMIPARAS

INITIALS	AGE	RACE	GRAVIDA	PARA	OTHER ALLERGY	PREVIOUS TOXEMIA	SKIN TEST: TOXIC GLOBULIN	MONTH OF GESTATION	REMARKS
A. H.	20	N	i	0	0	0	0	3	Hyperemesis
L. A.	23	W	i	0	0	0	0	5	Pyelitis
G. R.	22	W	i	0	0	0	0	5	
N. B.	22	W	i	0	0	0	0	6	
C. B.	18	N	i	0	0	0	0	6	
J. R.	22	N	i	0	0	0	1+	7	
M. M.	21	W	i	0	0	0	0	7	
C. A.	24	W	i	0	0	0	0	7	
L. A.	25	N	i	0	0	0	0	7	
O. I.	20	W	i	0	0	0	1+	8	
C. E.	19	N	i	0	0	0	0	8	Cystitis
M. V.	25	N	ii	0	0	0	2+	9	
G. R.	25	N	i	0	0	0	1+	9	Essential hypertension
M. R.	20	N	i	0	0	0	1+	9	
N. S.	17	N	i	0	0	0	0	9	
M. B.	25	N	ii	0	0	0	0	9	
S. M.	20	N	i	0	0	0	0	9	
D. K.	21	W	i	0	0	0	0	9	
D. H.	25	N	ii	0	0	0	2+	9	
H. A.	24	W	i	0	0	0	0	9	
N. S.	17	N	i	0	0	0	0	9	
					Per cent positive		28		

Results

The trends noted in our cutaneous sensitivity reactions were striking enough to warrant this preliminary report.

The placental globulin extracted from a toxemic placenta showed 43 per cent positive skin reactions in 187 patients. Commercial immune gamma globulin showed 17 per cent allergic reactions in 97 patients.

In cases of pre-eclampsia and eclampsia, the toxic globulin extract gave 83 per cent positive reactions while the immune globulin extract was found to give 7 per cent positive reactions.

The positive reactions to commercial immune globulin were highest in nonpregnant subjects (nulligravidas and nonpregnant gravidas, the latter referring to women who have been pregnant in the past, not necessarily to term, but who are not pregnant at the time of testing), namely, 33 and 37 per cent, respectively. Patients with early interrupted pregnancies (spontaneous abortions and ectopic pregnancies) showed 28 per cent positive reactions. There were no positive tests in males and only 4 per cent positives in postpartum patients.

The sensitivity to toxemic placental globulin was noted to be high in the cases of nulligravidas (67 per cent) and nonpregnant gravidas (88 per cent). During pregnancy, the proportion of sensitive individuals appeared to be lower, namely 48 per cent in early spontaneous abortions and ectopic pregnancies and an average of 29 per cent in uncomplicated antepartum patients. There appeared to be an increase in positive reactions to toxemic globulin in normal patients as pregnancy progressed, so that in the first trimester (two cases) there were no positives. In the second trimester there were 17 per cent positive in 12 cases, and in the third trimester 34 per cent positive tests in 41 patients.

A further breakdown of the results in normal cases in the last trimester also showed increasing percentages of positive reactions to toxemic globulin as pregnancy progressed to term. These figures are shown, with comparative toxemic cases, in Table II.

TABLE VIII. CONTROLS: ANTEPARTUM MULTIPARAS

INITIALS	AGE	RACE	GRAVIDA	PARA	OTHER ALLERGY	PREVIOUS TOXEMIA	SKIN TEST: TOXIC GLOBULIN	MONTH OF GESTATION	REMARKS
D. S.	30	W	iv	i	0	0	0	2	Hyperemesis
L. I.	30	N	iii	i	0	0	0	4	
L. M.	28	W	iii	ii	0	0	0	5	
A. C.	36	W	viii	vi	0	0	3+	5	
K. P.	29	N	iii	ii	0	0	1+	6	
E. D.	38	N	v	iii	0	0	0	6	Pyelitis
H. G.	25	W	iii	ii	0	0	0	6	
H. T.	27	W	vi	v	0	0	0	6	
M. S.	23	N	v	iii	0	0	0	6	
F. L.	24	N	v	iv	0	0	3+	7	Twins
R. B.	32	N	iv	ii	0	0	1+	7	Toxemia later
C. L.	25	W	iv	i	0	0	0	7	Pyelitis
J. B.	30	N	iv	iii	0	0	0	7	
L. C.	27	N	v	iii	0	0	0	7	
M. M.	39	W	ix	vii	0	0	0	7	
B. B.	19	N	ii	i	0	0	0	7	
J. A.	30	N	iv	iii	0	0	0	7	
C. C.	28	W	ii	i	0	0	0	7	
M. E.	28	N	ii	i	0	+	0	7	
L. H.	26	N	v	iii	0	+	0	8	
M. G.	22	W	iii	ii	0	0	0	8	
N. J.	21	N	ii	i	0	0	1+	8	
E. A.	20	N	ii	i	0	+	0	8	Pyelitis
V. G.	21	N	iv	iii	0	0	0	8	
A. D.	27	N	ii	i	0	0	2+	9	
J. S.	23	N	ii	i	0	0	4+	9	
L. K.	27	N	ii	i	0	0	1+	9	
M. C.	24	W	ii	i	0	+	1+	9	Twins
N. J.	21	N	ii	i	0	0	0	9	
B. L.	29	W	iii	ii	0	0	3+	9	
M. S.	42	W	iii	ii	0	0	0	9	
M. J.	30	N	iii	i	0	0	0	9	
O. C.	30	Y	iii	i	0	0	0	9	
P. C.	20	N	ii	i	0	0	0	9	
					Per cent positive		30		

Most of the toxemic patients showed persistent, positive reactions during the duration of their hospital stay, though some gave a diminished intensity of skin reaction several days post partum. When the severity of the toxemia cases, judged clinically, was correlated with the frequency of positive skin

TABLE IX. CONTROLS: POSTPARTUM WOMEN

INITIALS	AGE	RACE	GRAVIDA	PARA	OTHER ALLERGY	PREVIOUS TOXEMIA	DAYS POSTPARTUM	SKIN REACTIONS	
								TOXIC GLOBULIN	IMMUNE GLOBULIN
G. H.	16	N	i	i	0	0	1	0	0
							4	0	0
G. S.	18	N	i	i	0	0	1	2+	0
							4	1+	0
P. B.	32	W	i	i	0	0	1	1+	0
							4	1+	0
D. D.	19	N	i	i	0	0	1	0	0
							4	0	0
A. O.	22	W	i	i	0	0	1	0	1+
							4	0	0
P. F.	27	W	i	i	0	0	1	1+	0
							4	1+	0
D. K.	17	N	i	i	0	0	1	0	0
							4	0	0
B. M.	20	N	ii	i	0	0	1	0	0
							4	0	0
D. H.	29	N	ii	i	0	0	1	0	0
							4	0	0
S. G.	19	N	ii	ii	0	+	1	0	0
							4	0	0
M. C.	20	W	ii	ii	0	0	1	0	0
							4	0	0
J. P.	22	N	ii	ii	0	0	1	0	0
							4	0	0
J. M.	18	W	ii	ii	0	0	1	0	0
							4	0	0
V. C.	40	N	ii	ii	0	+	1	2+	1+
							3	2+	1+
							6	2+	1+
M. G.	22	W	ii	ii	0	0	1	0	0
							4	0	0
R. G.	22	N	iii	iii	0	0	1	0	0
							4	0	0
M. V.	19	W	iii	iii	0	0	1	0	0
							4	0	0
A. B.	21	N	iii	iii	0	0	1	0	0
							4	0	0
V. B.	28	W	iv	iii	0	0	1	1+	0
							4	1+	0
V. M.	26	N	iv	iv	0	0	1	0	0
							4	0	0
M. S.	24	W	v	iv	0	0	1	0	0
							4	0	0
C. P.	23	W	v	iv	0	0	1	0	0
							4	0	0
M. R.	30	W	v	v	0	0	1	0	0
							4	0	0
C. E.	35	N	vi	v	0	0	1	0	0
							4	0	0
H. W.	24	N	vi	vi	0	0	1	0	0
							4	0	0
						Per cent positive		20	4

TABLE X. PATIENTS WITH TOXEMIA OF PREGNANCY

INITIALS	AGE	RACE	GRAVIDA	PARA	DIAGNOSIS	MONTH OF GESTATION	OTHER ALLERGY	PREVIOUS TOXEMIA	SKIN TESTS		MAXIMUM BLOOD PRESSURE	REMARKS
									TOXIC GLOBULIN	IMMUNE GLOBULIN		
S. T.	28	N	vi	v	Pre-ecl., severe	8	0	+	4+	0	180/100	Prem. sep. of placenta
R. S.	23	N	ii	i	Pre-ecl., severe	8	0	+	3+	0	200/100	
									1+	0		
P. R.	17	N	i	0	Pre-ecl., severe	9	0	0	2+		200/100	
									1+			
R. P.	38	N	ii	i	Pre-ecl., severe	7	0	0	4+		200/116	Prem. sep. of placenta
Z. D.	19	N	i	0	Eclampsia	9	0	0	4+		170/120	Twins
A. W.	22	N	iii	ii	Pre-ecl., severe	7	0	+	4+		160/100	Hydronephrosis
									4+			Second test: 11 days post partum
R. B.	32	N	iv	ii	Pre-ecl., severe	8	0	+	2+		190/110	Second test: 12 days post partum
									0			
R. S.	27	W	i	0	Pre-ecl., severe	7	0	0	4+		190/110	
P. N.	30	W	i	0	Pre-ecl., severe	9	0	0	4+		170/120	
M. M.	20	W	i	0	Pre-ecl., severe	9	0	0	3+		190/120	
E. P.	28	W	i	0	Pre-ecl., mod.	9	0	0	3+	0	170/100	
									1+	0		
A. B.	26	N	i	0	Pre-ecl., mod.	9	0	0	1+	0	150/100	
									1+	0		
A. E.	23	W	i	0	Pre-ecl., mod.	9	0	0	4+	0	150/100	
									2+	0		
									0	0		
B. J.	18	W	i	0	Pre-ecl., mod.	9	0	0	2+	1+	136/100	
									1+	1+		
A. J.	40	N	i	0	Pre-ecl., mod.	7	0	0	4+		140/90	Prem. sep. of placenta
									1+			
N. W.	17	N	i	0	Pre-ecl., mod.	7	0	0	1+	0	160/110	Prem. sep. of placenta
									1+	0		
J. M.	36	N	v	iv	Pre-ecl., mod.	9	0	+	1+	0	175/100	
									0	0		
									0	0		

L. L.	28	W	ii	0	Pre-ecl., mod.	7	0	0	2+		156/96	Possible chronic nephritis
									0			
I. T.	25	N	ii	0	Pre-ecl., mod.	8	0	0	2+		170/100	
M. R.	31	W	i	0	Pre-ecl., mod.	5	0	0	4+		145/80	Possible chronic nephritis
P. R.	21	W	ii	i	Pre-ecl., mod.	7	0	+	2+		150/110	Possible chronic nephritis
M. K.	33	W	i	0	Pre-ecl., mod.	8	0	0	1+		170/80	
T. B.	18	W	i	0	Pre-ecl., mild	9	0	0	0	0	160/100	
									1+	0		
T. B.	19	N	i	0	Pre-ecl., mild	8	0	0	2+	0	140/90	
									2+	0		
L. J.	33	N	i	0	Pre-ecl., mild	8	0	0	0	0	140/90	
F. C.	21	N	i	0	Pre-ecl., mild	8	0	0	0	0	150/100	Possible chronic nephritis
									0	0		
C. W.	28	W	iii	ii	Pre-ecl., mild	7	0	0	0	0	150/90	Prem. sep. of placenta
									0	0		
A. H.	23	W	i	0	Pre-ecl., mild	9	0	0	4+	0	130/95	
									1+	0		
									1+	0		
D. F.	26	W	i	0	Pre-ecl., mild	9	0	0	0		160/104	
V. N.	21	N	ii	0	Pre-ecl., mild	8	0	0	2+		140/96	
J. B.	28	W	vi	iv	Pre-ecl., mild	9	0	+	1+		130/90	
E. T.	24	N	ii	i	Pre-ecl., mild	9	0	+	2+		130/100	
H. S.	21	N	ii	i	Pre-ecl., mild	9	0	0	2+		160/96	
A. H.	23	N	i	0	Pre-ecl., mild	7	0	0	0		170/120	Stillbirth
B. R.	25	W	i	0	Pre-ecl., mild	9	0	0	1+		130/96	
							Per cent positive		83	7		
E. C.	21	N	iii	i	Essential hypertension with pre-eclampsia	8	0	0	3+	0	170/100	
									2+			
C. C.	23	W	i	0	Essential hypertension with pre-eclampsia	8	0	0	3+		200/120	
M. C.	37	W	i	0	Essential hypertension with pre-eclampsia	7	0	0	0		170/110	
							Per cent positive		66	0		

TABLE X.—CONT'D

INITIALS	AGE	RACE	GRAVIDA	PARA	DIAGNOSIS	MONTH OF GESTATION	OTHER ALLERGY	PREVIOUS TOXEMIA	SKIN TESTS		MAXIMUM BLOOD PRESSURE	REMARKS
									TOXIC GLOBULIN	IMMUNE GLOBULIN		
E. H.	24	W	i	0	Essential hypertension	9	0	0	0		154/100	
P. T.	31	N	v	iii	Essential hypertension	9	0	0	0		180/120	
E. T.	25	N	v	iv	Essential hypertension	8	0	0	0 0	0 0	160/100	
G. J.	19	N	ii	i	Essential hypertension	8	0	+	0 0	0 0	145/95	
E. B.	23	N	i	0	Essential hypertension	8	0	0	0 0	0 0	170/110	
P. S.	24	N	iv	iii	Essential hypertension	8	0	0	0		170/110	
L. P.	30	N	i	0	Essential hypertension	6	0	0	4+ 4+	0 0	190/130	
G. B.	20	N	i	0	Essential hypertension	9	0	0	0		160/94	
O. M.	27	N	vi	v	Essential hypertension	9	0	0	0		150/100	
A. L.	16	N	i	0	Essential hypertension	8	0	0	3+		160/100	
S. Y.	26	W	i	0	Essential hypertension	4	0	0	4+		150/70	Erythema nodosum
							Per cent positive		27	0		
A. B.	39	W	iv	ii	Chronic nephritis	9	0	+	1+		160/100	
M. M.	27	W	vi	0	Chronic nephritis	8	0	+	4+		165/120	
D. P.	23	N	iv	0	Chronic nephritis	9	0	+	0		160/100	
S. R.	31	W	iii	iii	Chronic nephritis	7	+	+	1+		160/100	Erythroblastosis
M. S.	26	N	ii	ii	Chronic nephritis	5	0	+	4+		190/110	
							Per cent positive		80			

reactions to the toxic globulin extract, it was found that the mild cases gave 61 per cent positives, the moderate toxemias 92 per cent, and the severe cases 100 per cent positive reactions (Table XI). Only 20 per cent positive reactions were found in the postpartum nontoxemic patients.

There was no essential difference between the number of positive reactions in multiparas as compared to primiparas. Several patients who received blood transfusions showed no definite difference in their skin tests done before and after the transfusion. Fever did not appear to alter significantly the skin reactions in patients in whom we had an opportunity to do tests in both the febrile and afebrile phases of the hospital stay. Of 10 patients who had a history of other allergy (and of whom only one was toxemic), 80 per cent had positive reactions to toxic globulin and 44 per cent of 9 cases showed positive reactions to immune globulin. In 22 patients with a history of previous toxemia, only 2 of the 9 nontoxemic cases, 22 per cent, were positive to toxemic globulin, while 25 per cent were positive to immune globulin.

Many of our cases of toxemia were of considerable interest when viewed with the clinical and skin sensitivity reactions both in sight, but their individual descriptions would require time and space beyond the scope of this article.

TABLE XI. COMPARISON OF REACTIONS TO TOXEMIC GLOBULIN IN PRE-ECLAMPSIA ACCORDING TO SEVERITY

	NUMBER OF CASES TESTED	PER CENT POSITIVE
Mild	13	61
Moderate	12	92
Severe	10	100

Comment

Allergies previously present become generally milder during pregnancy,[9] with the increased corticosteroids apparently causing much of this altered sensitivity. Several investigators[15a, 15b, 15c] have demonstrated a diminution in various intradermal reactions to antigens after the administration of cortisone and adrenocorticotropic hormone. Some time ago, Zinsser and coworkers[16] speculated on the antigenic effect of placental extract on the adrenal gland. Since then, several workers[17a, 17b] have clearly demonstrated the adrenocorticotropic activity of the human placenta.

In this study, we noted that the percentage of positive skin tests to toxemic placental globulin diminished as pregnancy began, but gradually increased toward term if the gestation proceeded normally and then dropped to its lowest level immediately post partum. However, there was greatly increased sensitivity to this toxic globulin extract in patients with toxemia and this persisted for at least one week post partum. We can postulate that there is present in toxemias either an increased allergy to this particular substance, or a failure of the normal immunologic mechanism. This failure could indicate not only a deficiency of antibodies or of proteolytic enzymes

and histaminase, but possibly also an overloading of the organism with a toxic allergen. According to accepted theories, allergy implies previous sensitization. It is difficult, however, to explain sensitization to placental globulins in a nullipara or a male as an allergic phenomenon, except by going back to fetal or neonatal life and presupposing a transplacental or lactational transfer of the identical protein as an immunizing mechanism. On the other hand, the positive skin test in pre-eclampsia may denote a toxin-sensitivity state, or lack of immunity, as seen in the Schick test with diphtheria toxin.

Since the positive response to toxic globulin in toxemias was found in chronic nephritis as well as in pre-eclampsia, we can conclude that this test would not have significance as an aid in the differential diagnosis of the various forms of toxemia of pregnancy. Similarly, the test would not be an index to the severity of pre-eclampsia, for, even though the severe cases always showed positive skin reactions, the mild cases individually showed some strongly positive and some negative reactions. Furthermore, most obstetricians know from practical experience that all toxemias are potentially severe. We have as yet done no detailed studies on when sensitivity to this toxic placental extract appears, and cannot state with a sufficient degree of certainty whether or not toxemia can be predicted by the finding of an early positive reaction. It should be noted that the positive reactions in normal women increase progressively toward term. Most of the patients with positive reactions found in the prenatal clinic, however, completed their pregnancies without the development of toxemia. At one stage of our work, it appeared that the loss of sensitivity to toxemic globulin early in pregnancy might serve as a test for pregnancy, but our results showed too low a correlation to give sufficient accuracy.

Further investigation is warranted along the lines of this study, particularly an attempt at the isolation of the specific factor in the toxemic globulin from a large number of pooled toxemic placentas.

Summary and Conclusions

1. Extracts of our toxemic placental globulin gave a high proportion of positive skin reactions in patients with toxemia of pregnancy as compared to normal pregnancy.

2. Nulligravidas and nonpregnant gravidas showed a high percentage of positive reactions to our toxemic placental globulin extract. In normal pregnancy, this sensitivity diminished early in the gestation, rose gradually toward term, and then dropped to low levels again in the puerperium.

We are indebted to Drs. Milton Goodfriend and Samuel S. Rosenfeld for their encouragement and for making available their private and service cases for study; also to Drs. Harry Gordon, William LaVine, and Irving Terman for permitting us to do testing on several of their private patients. The toxic globulin extract of placenta was prepared by E. Murrow and S. Shapiro of the U. S. Vitamin Corporation Laboratories, Yonkers, N. Y., to whom, also, we owe our appreciation. We are very grateful to Dr. Joseph C. Ehrlich for many valuable criticisms and suggestions.

References

1. Page, E. W.: Survey 3: 615, 1948.
2. Dieckmann, W. J.: The Toxemias of Pregnancy, ed. 2, St. Louis, 1952, The C. V. Mosby Company.
3. Hunt, H. F., Patterson, W. B., and Nicodemus, R. E.: Am. J. Clin. Path. 10: 319, 1940.
4. Schneider, C. L.: Surg., Gynec. & Obst. 90: 613, 1950.
5. Smith, G. V., Smith, O. W., and Romney, S. L.: AM. J. OBST. & GYNEC. 63: 1185, 1952.
6. Yamada, K. I.: Jap. J. Obst. & Gynec. 23: 2, 1940.
7. Junghans, E.: Arch. f. Gynäk. 168: 656, 1939.
8. Jegorov, B. A.: (a) Zentralbl. f. Gynäk. 58: 2851, 1934.
   (b) Zentralbl. f. Gynäk. 59: 465, 1935.
9. Urbach, E., and Gottlieb, P. M.: Allergy, ed. 2, New York, 1946, Grune & Stratton.
10. (a) Kaku, M., Hashimoto, Y., Takeda, T., Matsumoto, K., and Iwamoto, Y.: Kumamoto M. J. 4: 75, 1951.
    (b) Kaku, M.: J. Obst. & Gynaec. Brit. Emp. 60: 148, 1953.
11. Youssef, A. F., and Barsoum, G. S.: J. Obst. & Gynaec. Brit. Emp. 60: 388, 1953.
12. Lin, H. A. C.: AM. J. OBST. & GYNEC. 54: 97, 1947.
13. Hoffman, D. B.: AM. J. OBST. & GYNEC. 58: 385, 1949.
14. Lapan, B.: Unpublished data.
15. (a) Osgood, C. K., and Favour, C. B.: J. Exper. Med. 94: 415, 1951.
    (b) Vollmann, H.: J. Pediat. 39: 22, 1951.
    (c) Bordley, J. E., et al.: Bull. Johns Hopkins Hosp. 85: 396, 1949.
16. Zinsser, H. H., Zinsser, A. D., and Storey, C. M.: Arch. Path. 50: 606, 1950.
17. (a) Jailer, J. W., and Knowlton, A. I.: J. Clin. Investigation 29: 1430, 1950.
    (b) Opsahl, J. C., and Long, C. N. H.: Yale J. Biol. & Med. 24: 199, 1951.

1882 GRAND CONCOURSE

ADRENOCORTICAL FUNCTION IN TOXEMIA OF PREGNANCY*

ELEANOR H. VENNING, PH.D., BERTHA SINGER, PH.D., AND
GEORGE A. SIMPSON, M.D., MONTREAL, QUEBEC

(From the McGill University Clinic, Royal Victoria Hospital, and the Department of Obstetrics and Gynecology, Royal Victoria Hospital)

MANY hypotheses have been advanced to explain the pathogenesis of the late toxemias of pregnancy. Consistent findings of excessive gain in weight, appearance of edema, increasing blood pressure, and proteinuria suggest the presence of abnormal amounts of substances which directly influence electrolyte and fluid balance.

Hormonal factors such as the antidiuretic substance and the adrenocortical steroids play an important role in the regulation of the metabolism and distribution of body water. In the present study we have been interested primarily in the variations in adrenocortical function in the normal pregnant woman and in patients with toxemia of pregnancy.

Observations made throughout normal pregnancy reveal that there is increased activity of the adrenal cortex as evidenced by the enlargement of the adrenal glands and the presence of increased amounts of adrenocortical metabolites in the urine. Using a bio-assay, Venning[1] has reported an elevation in the level of urinary glucocorticoids in the last trimester of pregnancy. Tobian,[2] Lloyd and co-workers,[3] Parviainen and associates,[4] Devis,[5] and Jailer,[6] with chemical procedures, have observed a similar rise in the urinary corticoids in normal pregnancy. These investigators have reported finding a still higher output of corticoids in toxemia of pregnancy. Chart, Shipley, and Gordon[7] found no significant rise in formaldehydogenic steroids in toxemia of pregnancy but showed that the steroidal fraction in this disease had a marked effect on sodium retention. They suggested that this abnormality in the pattern of excretion of corticoids might explain all of the clinical manifestations of this syndrome.

Selye's[8] hypothesis that eclampsia may be the result of continued hyperfunction of the adrenal cortex, caused by stress, has received support from the following investigators, Ordman,[9] Schuurmans,[10] Garrett,[11] and Parviainen and collaborators.[12] These authors have assumed that the abnormality lies in the response of the adrenal cortex of the mother to the emotional and physical stresses of pregnancy rather than in that of the fetus.

In an effort to determine the participation of the adrenal cortex in the development of this syndrome, the output of free and conjugated formaldehydogenic steroids has been measured in normal pregnant women and in pa-

*Supported in part by grants from the National Research Council of Canada and the Obstetrical and Gynecological Research Fund.

tients showing clinical manifestations of toxemia of pregnancy. In addition, the effect of these steroids upon carbohydrate metabolism and sodium retention have been investigated.

Clinical Material

Only those patients who developed toxemia between the seventh and ninth months of pregnancy were studied. They were classified clinically as having mild, moderate, or severe cases according to the criteria of the American Committee.[13] Similar investigations were carried out during the same period in normal pregnancy. Seventeen normal pregnant women and 43 with toxemia of pregnancy were followed. In addition 6 cases of pregnancy with hypertension were included in this investigation.

Methods

Formaldehydogenic Steroids.—In order to determine the effect of toxemia upon the conjugation of the corticoids, two groups of corticoids were measured, the "free" fraction and those conjugated as glucuronides. The "free" fraction was obtained as follows. The urine was acidified to pH 1 and extracted immediately with chloroform. The chloroform extract was washed with alkali and water and taken to dryness. The conjugated fraction was obtained following the hydrolysis of the urine with the enzyme β-glucuronidase and was extracted as described above. Both fractions were measured by a modification of the method of Daughaday, Jaffe, and Williams.[14] This method determines corticoids having a primary α-ketol side chain at C_{17} and includes the active corticoids plus the much larger quantities of inactive metabolites. As frequently it was not possible to obtain complete 24 hour urine collections of all the patients, the excretion of these corticoids is expressed as milligrams of formaldehydogenic steroids excreted per gram creatinine.

Glucocorticoids.—These were determined by the bioassay method of Venning and associates[15] on the "free" neutral fraction. This assay is a measure of activity of the extracts on carbohydrate metabolism. Cortisone was used as the standard.

Sodium-Retaining Steroids.—The sodium-retaining effect of the urinary metabolites was estimated on the crude fraction, using the method of Singer and Venning.[16] Radioactive sodium is administered along with the extract to be tested, to fasted adrenalectomized rats and the rate of excretion of Na^{24} is determined. As this crude fraction contains many steroids, some of which are sodium retaining and others sodium excreting, the net result will be a balance between the various hormones. The results are therefore expressed as a percentage of the excretion of Na^{24} of the control animals, rather than in terms of a standard, i.e., desoxycorticosterone. The excretion of Na^{24} by the control group of animals is taken as 100 per cent. If the extracts cause a retention of Na^{24} then the values will be below 100.

Results

The values obtained for the excretion of formaldehydogenic corticoids in 17 cases of normal pregnancy ranged from 0.57 mg. to 2.18 mg. per gram creatinine for the free fraction, with a mean of 1.27 mg. Those for the conjugated fraction ranged from 9.8 to 42.2 mg. per gram creatinine with a mean of 21.0 mg. These findings are listed in Table I and individual values in the different groups of patients are charted in Figs. 1 and 2. There was considerable overlapping of values in all five groups of patients and the range was

greater in the patients with toxemia than in the normal cases. A progressive increase was observed in the mean value for both the free and conjugated corticoids in those patients with mild and moderate toxic symptoms, the mean values for the free neutral fraction being 2.42 mg. and 3.04 mg. per gram creatinine, and those for the conjugated fraction being 29.2 mg. and 36.6 mg.

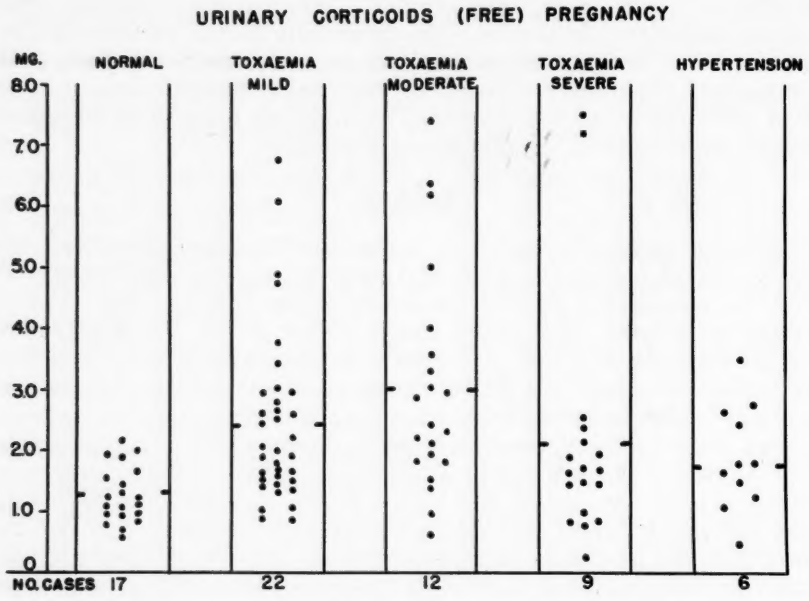


Fig. 1.—Formaldehydogenic steroids extracted at pH 1. Urinary corticoids are expressed as milligrams of cortisone excreted per gram of creatinine.

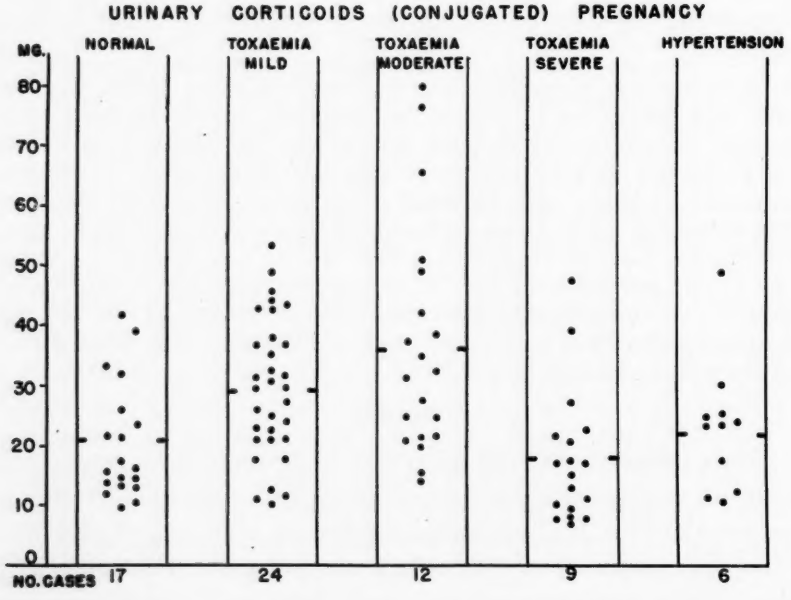


Fig. 2.—Formaldehydogenic steroids extracted after beta-glucuronidase hydrolysis. Urinary corticoids are expressed as milligrams of cortisone excreted per gram of creatinine.

per gram creatinine, respectively. Compared with the normal values, these differences were of statistical significance. In the nine patients with severe toxic manifestations, the mean value for the corticoid excretion was lower than those found in the milder cases, 2.13 mg. per gram creatinine for the free neutral fraction and 17.7 mg. for the conjugated fraction. The patients with hypertension gave values only slightly higher than those found in the normal cases, 1.91 mg. and 23.5 mg. per gram creatinine for the two fractions.

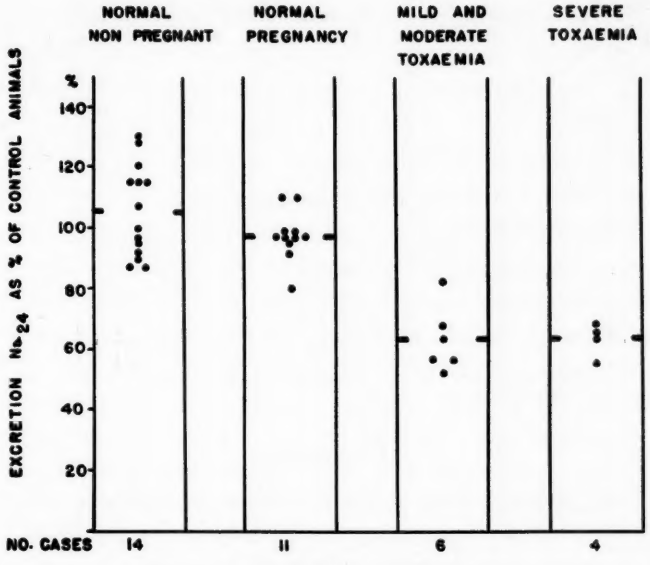


Fig. 3.—Sodium-retaining factor.

A different trend was observed in the excretion of glucocorticoids. These findings are listed in Table II. Here the majority of normal pregnancies showed a higher level of excretion of these active substances than the toxic patients. The normals ranged from 61 to 260 gamma cortisone equivalents per 24 hours with a mean value of 122 gamma. In 14 patients with mild toxemia of pregnancy, the range was from 38 to 105 gamma per 24 hours, and in 5 patients with moderate toxemia, from 36 to 63 gamma per 24 hours. Only 4 patients with severe toxemia were studied. In these the glucocorticoids were at approximately the same level as those found in the mild and moderate cases.

The sodium-retaining effect of the crude urinary extract was measured in nonpregnant women, normal pregnancy, and toxemia of pregnancy and the results are charted in Fig. 3. In nonpregnancy and normal pregnancy this fraction had little effect on the sodium metabolism of the adrenalectomized rat. Extracts obtained from all the patients with toxemia of pregnancy showed a sodium-retaining effect in this assay. Although there was no correlation between degree of sodium retention and severity of disease, the differences between the normal group and those with toxemia of pregnancy were of significance.

TABLE I. FORMALDEHYDOGENIC STEROIDS

	NO. OF PATIENTS	NO. OF DETERMINATIONS	MEAN (MG./GM. CREATININE)	STANDARD ERROR
Normal Pregnancy.—				
Free neutral fraction	17	20	1.27	±0.10
Conjugated fraction	17	19	21.0	±2.26
Mild Toxemia.—				
Free neutral fraction	22	34	2.42	±0.23
Conjugated fraction	22	33	29.2	±2.01
Moderate Toxemia.—				
Free neutral fraction	12	20	3.04	±0.44
Conjugated fraction	12	20	36.6	±3.80
Severe Toxemia.—				
Free neutral fraction	9	18	2.13	±0.48
Conjugated fraction	9	18	17.7	±0.69
Hypertension.—				
Free neutral fraction	6	11	1.91	±0.29
Conjugated fraction	6	11	23.5	±3.60

TABLE II. GLUCOCORTICOIDS

	NO. OF PATIENTS	RANGE	MEAN (μG/24 HOURS*)	STANDARD ERROR
Normal pregnancy	26	61-260	122	±10.6
Mild toxemia	14	38-105	65	± 5.5
Moderate toxemia	5	36-63	47	± 4.7
Severe toxemia	4	48-72	59	± 5.4

*Cortisone used as standard.

Comment

These findings suggest that there is both a qualitative and a quantitative change in the excretion of urinary corticoids in toxemia of pregnancy as demonstrated by an increase in total output of free and conjugated metabolites, a decrease in the steroids affecting carbohydrate metabolism, and a rise in the level of the sodium-retaining factor. Even in the early manifestations of this disease, where there is minimal edema or other toxic symptoms, these changes are observed in many of the patients. The most constant finding is an increase in the sodium-retaining effect of the extracts. As the severity of the disease increases, the total output of corticoids decreases. This is most noticeable in the conjugated fraction. As conjugation of the steroids with glucuronic acid is a function of the liver, the lower output of corticoid glucuronides might be the result of liver damage in these cases. In spite of the decrease in total output of corticoids, the sodium-retaining activity of the urinary extracts is increased.

Chart and his co-workers[7] also reported a rise in excretion of the sodium-retaining factor in toxemia of pregnancy and in one patient this was observed before clinical signs of toxemia had become apparent. Evidence for the presence of a highly active mineralocorticoid other than desoxycorticosterone in adrenal extracts and in adrenal venous blood has been presented by Simpson and Tait,[17] Simpson, Tait, and Bush,[18] and recently by Bush and associates[19] who have suggested that this substance may also be present in pregnancy urine. An increase in this sodium-retaining factor has also been demonstrated in uri-

nary extracts obtained from edematous patients with heart failure and nephrosis by Deming and Luetscher.[20] This effect was not observed in normals and nonedematous controls.

Selye's[8] hypothesis that toxemia of pregnancy may be regarded as a disease of adaptation caused by continued stimulation of the adrenal cortex is interesting in the light of these findings. It is difficult to prove whether the increased adrenocortical activity is the result of the disease or the cause of it. The fact that these abnormalities in adrenocortical function are already present at a time when clinical symptoms are minimal would support this hypothesis. Assuming that the urinary excretion reflects the activity of the gland, then the changes observed would lead to a retention of sodium and fluid in the body with a consequent rise in blood pressure.

It is interesting to speculate on the possibility of the placenta being the source of the corticoids in pregnancy. Evidence of a proteinlike hormone in the placenta with activity similar to ACTH has been put forward by Jailer,[6] Opsahl and Long,[21] and Böe and Salvesen.[22] Adrenal hormonelike activity has also been demonstrated in human and equine placental tissue by Johnson and Haines[23] in amounts equal to 0.3 mg. of hydrocortisone per kilogram of tissue.

The observation of a lowered output of cortisone-like steroids in toxemia of pregnancy suggests that cortisone might have a beneficial effect in this disease either through its direct action or indirectly through its suppression of the mineralocorticoid secretion. The number of patients with toxemia of pregnancy treated with cortisone is small and the results are conflicting. Moore and co-workers[24] and Tew and McAlpine[25] reported considerable clinical improvement in their series of cases. Jailer,[6] Caton, Reid, and Roby[26] and Agnew and associates[27] felt that the administration of cortisone had little modifying effect on the course of the toxemia. In all these cases, cortisone had been given only after other therapeutic measures had failed.

Summary

Adrenocortical function was investigated in 17 cases of normal pregnancy, 43 cases of toxemia of pregnancy, and 6 cases of pregnancy with hypertension.

Formaldehydogenic steroids, free and conjugated, were measured, as well as the glucocorticoids and the sodium-retaining factor.

There was a significant increase in the free and conjugated formaldehydogenic corticoids in the patients with mild and moderate symptoms. In the severe cases the mean value for the free fraction was lower than that found in the more moderate cases but still above that found in normal pregnancy. The conjugated fraction was, however, lower in the severe cases than in normal pregnancy.

The values found in the patients with hypertension were only slightly greater than those observed in normal pregnancy.

The sodium-retaining factor was increased in all the cases of toxemia. There was no correlation, however, between severity of symptoms and sodium-retaining effect.

The glucocorticoids were excreted at a lower level in the toxic patients than in normal pregnancy.

We wish to thank Miss Denise Girod for her valuable technical assistance, and the various nurses who have assisted in this study.

References

1. Venning, E. H.: Endocrinology 39: 203, 1946.
2. Tobian, L.: J. Clin. Endocrinol. 9: 319, 1948.
3. Lloyd, C. W., Hughes, E. C., Lobotsky, J., and Rienzo, J.: J. Clin. Endocrinol. 11: 786, 1951.
4. Parviainen, S., Soiva, K., and Vartiainen, S.: Acta obst. et gynec. Scandinav. 29: (Supp. 5) 1, 1950.
5. Devis, R., and Devis-vanden Eeckhoudt, M.: Ann. endocrinol. 11: 22, 1950.
6. Jailer, J. W.: Proc. Second Clinical ACTH Conference 1: 77, 1951.
7. Chart, J. J., Shipley, E. G., and Gordon, E. S.: Proc. Soc. Exper. Biol. & Med. 78: 244, 1951.
8. Selye, H.: J. Clin. Endocrinol. 6: 117, 1946.
9. Ordman, B.: South African M. J. 24: 938, 1950.
10. Schuurmans, R.: Brit. M. J. 1: 1016, 1951.
11. Garrett, S. S.: West J. Surg. 58: 229, 1950.
12. Parviainen, S., Soiva, K., and Vartiainen, S.: Acta. obst. et gynec. Scandinav. 29: 3, 1950.
13. American Committee on Maternal Welfare: The Mother 1: 14, 1940.
14. Daughaday, W. H., Jaffe, H., and Williams, R. H.: J. Clin. Endocrinol. 8: 166, 1948.
15. Venning, E. H., Kazmin, V. E., and Bell, J. C.: Endocrinology 38: 79, 1946.
16. Singer, B., and Venning, E. H.: Endocrinology 52: 623, 1953.
17. Simpson, S. A., and Tait, J. F.: Proc. Second Internat. Congress of Biochemistry, Paris, 1952, p. 137.
18. Simpson, S. A., Tait, J. F., and Bush, I. E.: Lancet 2: 226, 1952.
19. Bush, I. E., De Courcy, C., and Gray, C. H.: J. Endocrinol. 8: 12, 1952.
20. Deming, O. B., and Luetscher, J. A., Jr.: Proc. Soc. Exper. Biol. & Med. 73: 171, 1950.
21. Opsahl, J. C., and Long, C. N. H.: Yale J. Biol. & Med. 24: 199, 1951.
22. Böe, F., and Salvesen, S.: Lancet, 1: 1210, 1952.
23. Johnson, R. H., and Haines, W. J.: Science 116: 456, 1952.
24. Moore, H., Jessop, W. J. E., O'Donovan, D. K., Barry, A. P., Quinn, B., and Drury, M.: Brit. M. J. 1: 841, 1951.
25. Tew, W. P., and McAlpine, H. T.: Canad. M. A. J. 63: 287, 1950.
26. Caton, W., Reid, D., and Roby, C.: Science News Letter 59: 28, 1951.
27. Agnew, A. M., Palmer, R. A., Bagnall, A. W., and McIntosh, H. W.: Proc. Royal College of Physicians & Surgeons of Canada, 1952.

HEMANGIOPERICYTOMA OF THE UTERUS

PAUL PEDOWITZ, M.D., F.A.C.S., BROOKLYN, N.Y., LAURENCE B. FELMUS, M.D., F.A.C.S., NEW ROCHELLE, N. Y., AND DAVID G. GRAYZEL, M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, State University of New York at New York City, College of Medicine, and the Departments of Obstetrics, Gynecology, and Pathology, Jewish Hospital of Brooklyn)

BECAUSE of their relative rarity, vascular neoplasms of the uterus have received little attention in the literature, and most gynecologists are unfamiliar with these uterine tumors. A report of lymphangioma in a uterus removed by one of the authors (P. P.) prompted us to investigate this group of neoplasms. In addition, specimens previously diagnosed sarcoma or hemangioendothelioma were re-examined. It was discovered that two cases of "sarcoma" and two of "hemangioendothelioma" were, in reality, hemangiopericytomas.

This vascular tumor was first described by Stout and Murray[1] in 1942, and is characterized by numerous proliferating capillaries surrounded by round and ovoid cells, probably derived from pericytes. These cells were described and named by Zimmermann,[2] and are normally found in the outer surface of capillary walls. Although lacking myofibrils they nevertheless have contractile powers and bear a close relationship to smooth-muscle cells which they resemble. Pericytes are radially arranged around proliferating capillaries of a hemangiopericytoma, and are the essential component of the tumor.

Fisher, Kaufman, and Mason,[3] as well as Murray and Stout,[4] have grown cells obtained from a hemangiopericytoma in tissue culture. The former investigators noted not only the previously described pericytes, but also observed morphologic variants of the cells, similar to those seen in microscopic section of many hemangiopericytomas.

A notable difference between a hemangiopericytoma and a hemangioendothelioma is found in the appearance and behavior of the endothelial lining of the vessels of the tumor. In the latter neoplasm the endothelium reveals marked proliferation and presents a "heaped-up" appearance within the vascular sheaths, as well as invasion of the vessel wall and adjacent extravascular tissue (Fig. 1). In the former tumor the lining of the vessels does not vary from the normal. Pericytes do not invade vascular sheaths, although occasionally free nests of tumor cells have been observed within the lumen of a lymphatic channel (Fig. 11, *A*).

Other vascular tumors of the uterus, previously called perithelioma, were thought to arise from the endothelial lining of lymphatics within the adven-

titia of blood vessels. However, the concentric or radial arrangement of the cells of these tumors is strikingly similar to that observed in hemangiopericytoma, and it is likely that re-examination of original material would reveal many of these neoplasms to be the latter tumor.*

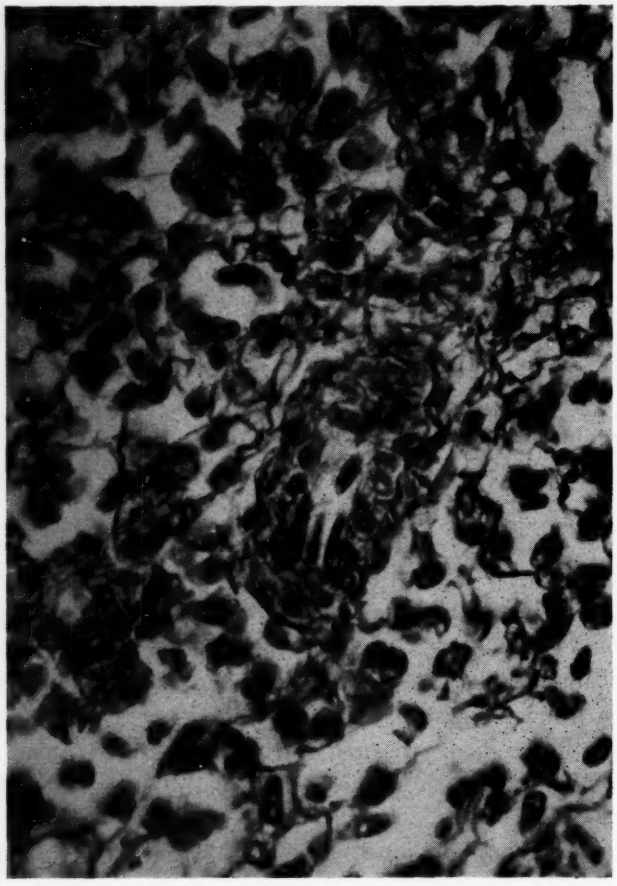


Fig. 1.—Hemangioendothelioma: "heaping-up" of endothelium within vascular sheath. (Wilder's reticulum stain. High power reduced ⅓.)

Description

Gross.—Hemangiopericytomas may have no characteristic distinguishing features (Fig. 2). Although of vascular origin and composed of numerous blood vessels, the tumors often vary from gray white to yellow in color, lacking the cyanotic red appearance usually associated with vascular new growths. This may be explained by the presence of numerous noncanalized proliferating capillaries within the tumor, as well as the absence of red cells within the patent vessels. Occasionally the blood channels do contain red cells, so that the tumor, in such instances, does exhibit the reddish coloration characteristic of vascular neoplasms.

*A review of all types of vascular neoplasms of the uterus is in preparation.

Hemangiopericytomas vary in size from microscopic lesions to tumors measuring 20 cm. or more in diameter. They may occur as solitary nodules or they may diffusely involve the uterine wall and extend by means of finger-like projections into the lymphatics and broad ligament. The smallest tumor in our series was 5 cm. in diameter, and the largest measured 12 cm. Three of the uterine growths were submucous and one was intramural but encroaching upon the endometrial cavity. Lacking a true capsule, marked difficulty is usually encountered during enucleation of these tumors from the uterus. In this respect they resemble leiomyosarcoma and adenomyoma.

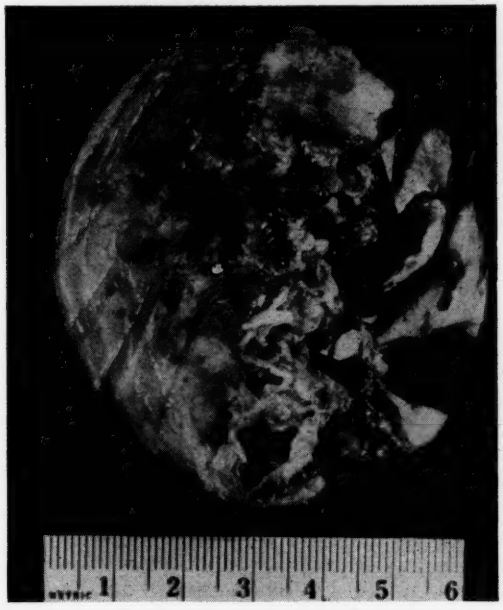


Fig. 2.—Hemangiopericytoma: section through uterus containing submucous tumor. Note absence of line of demarcation between tumor and adjacent myometrium.

Microscopic.—Microscopic examination is essential for diagnosis. Morphological variations exhibited by pericytes account for the frequently inconstant appearance presented by the tumor. The component cells may be round, ovoid, or spindle shaped and contain round or ovoid vesicular nuclei. The marked similarity of pericytes and smooth-muscle cells necessitates utilization of special differential stains, such as Masson's, to distinguish one from the other. This stain demonstrates the presence of connective tissue fibers between and around pericytes, as well as the absence of myofibrils in those cells. Since myofibrils are characteristic of smooth-muscle cells, the stain serves to differentiate them from pericytes. Whereas muscle tissue stains an orange-yellow color, pericytes stain green.

Typically, pericytes are concentrically arranged around the capillaries of the neoplasm. Although careful examination will almost always reveal areas of proliferating capillaries, the blood vessels may not be apparent in other areas when stained with hematoxylin and eosin. They are frequently non-

canalized or compressed by profusion of pericytes, but their presence can usually be demonstrated by application of silver stain. With this technique the sheaths of the blood vessels stain black, so that the extraluminal position of the pericytes is emphasized. In addition, connective-tissue septa are noted enveloping both large and small aggregates of cells, and, occasionally, isolated pericytes. Not only do vascular sheaths differ in thickness, but the reticulum content of the tumor also varies (Figs. 3 through 10).

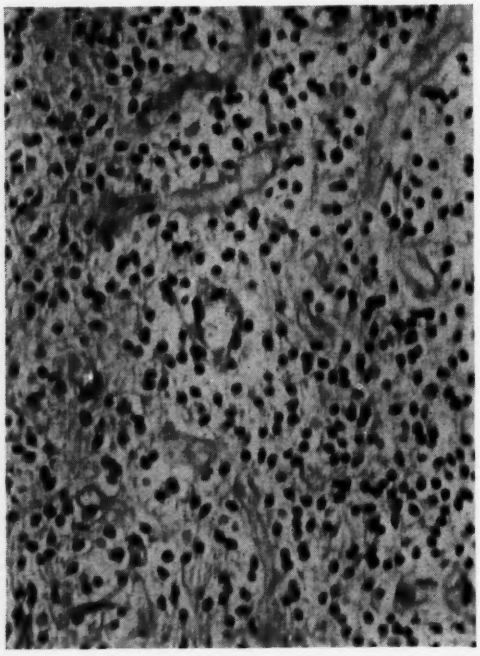


Fig. 3.—Hemangiopericytoma: concentric arrangement of pericytes around capillaries. (Hematoxylin and eosin. High power, reduced ⅙.)

Mitotic figures in hemangiopericytomas are rare, and when present in large numbers signify rapid growth and possible future malignant course. Mitoses were not observed in any of the cases in this series, although one case was obviously clinically malignant, terminating fatally, and another had a later recurrence of the growth.

Occasionally nests of tumor cells are observed lying free within lymphatic channels (Fig. 11, *A*), but the significance of this finding as an indication of malignancy is questionable.

Clinical Features

Review of case histories of patients with hemangiopericytoma fails to reveal any characteristic or distinctive signs or symptoms (Table I). Abnormal vaginal bleeding can be attributed to submucous location of the growths (the intramural tumor of Case 1 had encroached upon the endometrial cavity). The patients ranged in age from 25 to 77 years; the parity varied from 0 to 3.

The uterus was found to be enlarged in two patients, and a diagnosis of submucous fibroids was made in the remaining two. Enucleation of the tumor

of Case 1 required sharp dissection for its separation from the adjacent myometrium, and the laboratory report was "cellular myoma or possible early sarcoma." Six months after this initial "myomectomy" uterine enlargement was again noted, progressively increasing during the succeeding 2½ years, when hysterectomy was finally performed. The tumor within the uterus was found to be identical with the neoplasm removed by enucleation 3 years before (Figs. 5 and 6).

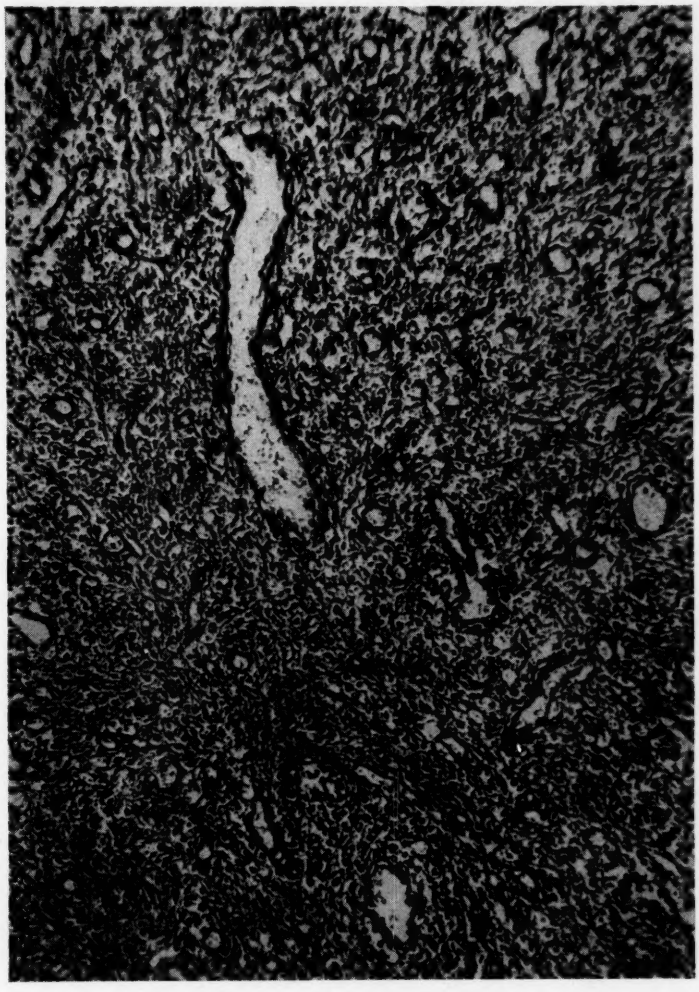
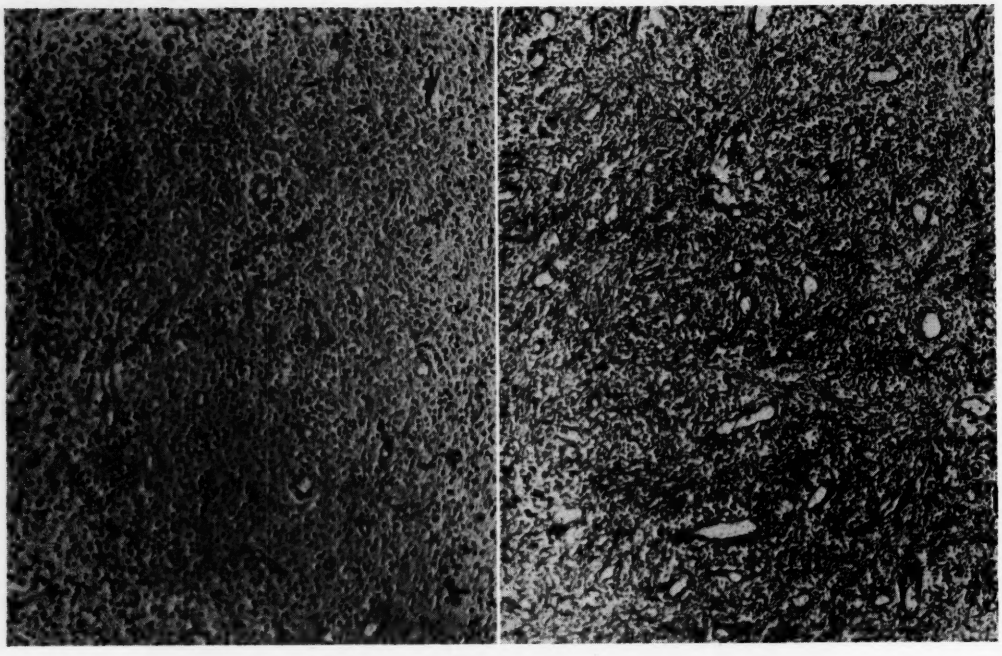


Fig. 4.—Extravascular distribution of pericytes; capillaries lined with normal endometrium. (Wilder's reticulum. Medium power, reduced ¼.)

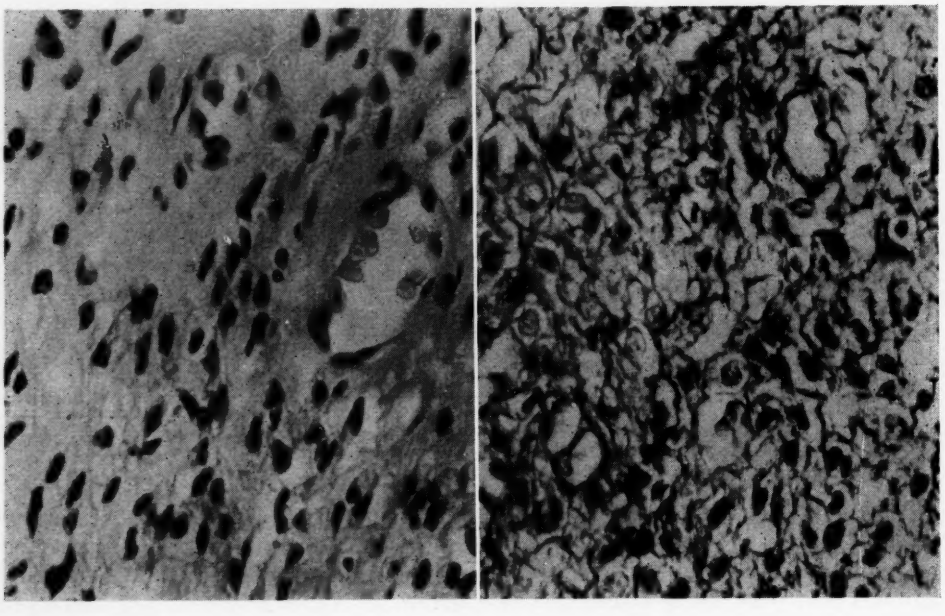
Postoperative radiation therapy was given to the 4 patients. Three were alive and well 6, 8, and 11 years after operation, despite a local recurrence of the tumor in one of the patients. The sole death occurred 18 months after the diagnosis was first made and 4½ years after the appearance of postmenopausal bleeding.

This patient was a 77-year-old white woman who was admitted to the hospital in 1950 for recurrence of the vaginal bleeding. Diagnostic curettages in 1947 and 1948 had revealed



A. *B.*

Fig. 5 (Case 1).—*A*, Hemangiopericytoma showing apparent vascularity. (Hematoxylin and eosin. Medium power. reduced ⅙.) *B*, Previously occult vessels made visible by reticulum stain. (Wilder's stain. Medium power, reduced ⅙.)



A. *B.*

Fig. 6 (Case 1).—*A*, Recurrent tumor. Compare with Fig. 5, *A* and *B*. (Hematoxylin and eosin. Medium power, reduced ⅓.) *B*, Recurrent tumor. (Wilder's reticulum. Medium power, reduced ⅓.)

an atrophic endometrium. Although she received postoperative x-ray therapy in adequate dosage after each dilatation and curettage, she continued to have recurrent episodes of vaginal bleeding, and because of severe hypertension associated with arteriosclerotic heart disease

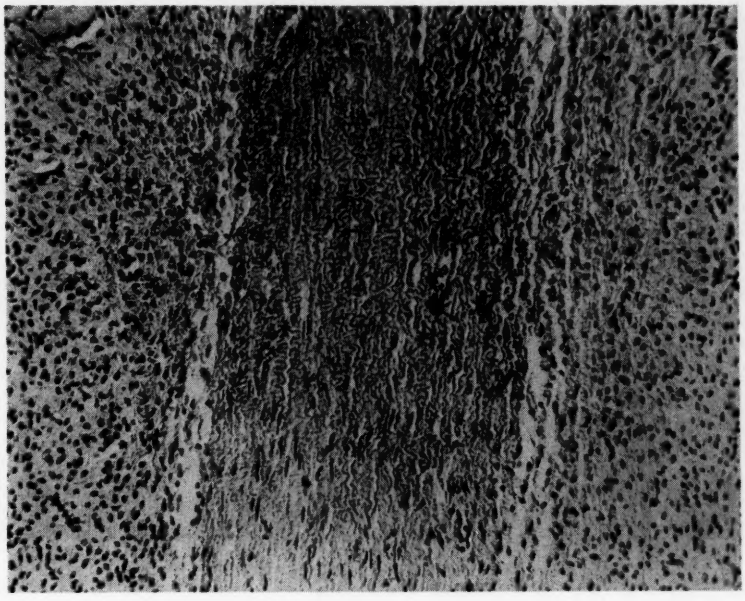
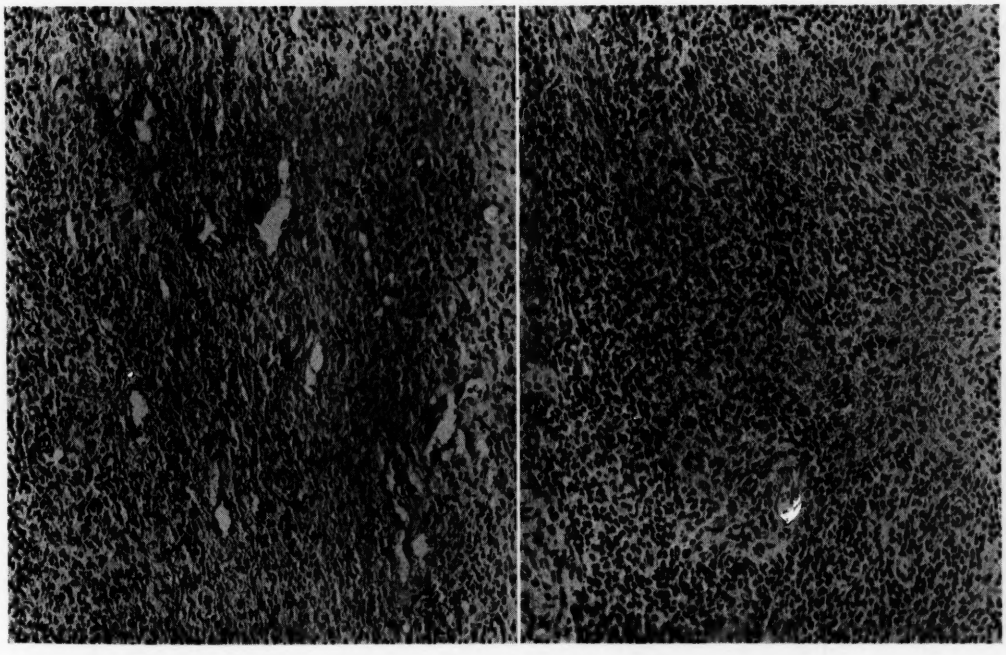
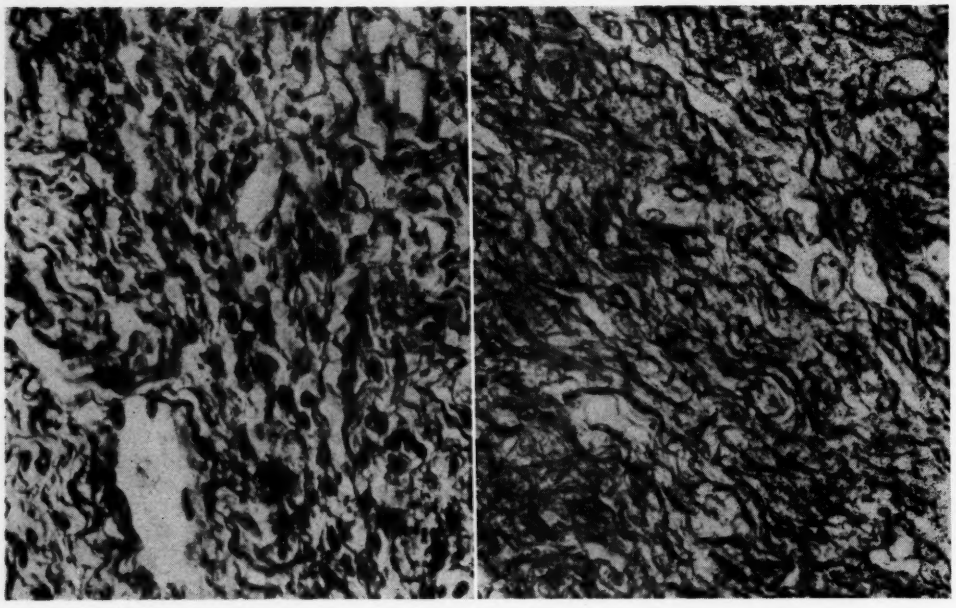


Fig. 7.—Invasion of myometrium by tumor cells. (Hematoxylin and eosin. Medium power, reduced ⅙.)



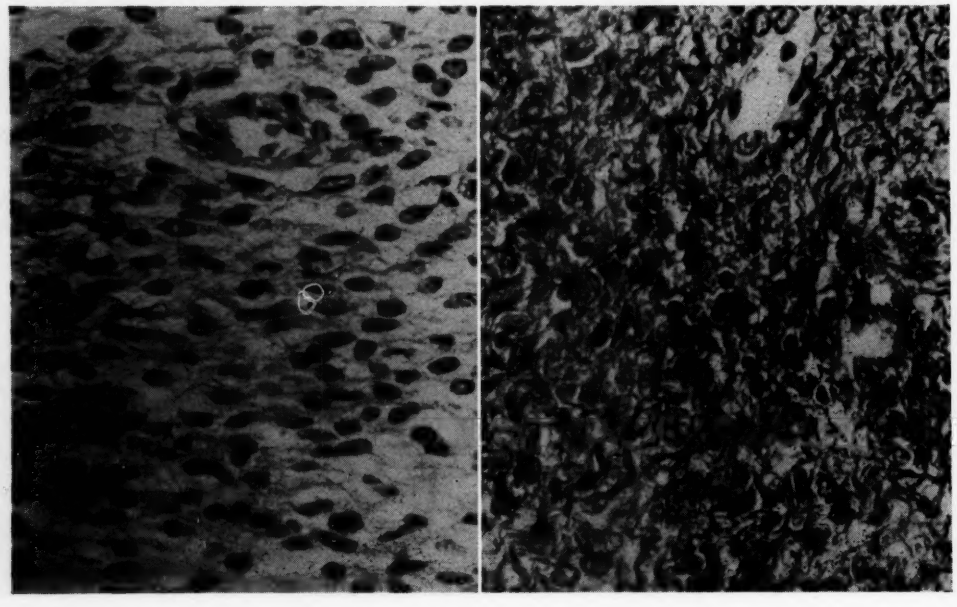
A. *B.*

Fig. 8 (Case 2).—*A*, Section of tumor exhibiting vascularity. (Hematoxylin and eosin. Medium power, reduced ⅙.) *B*, Another area of same tumor. Note marked cellularity and lack of apparent blood vessels. (Hematoxylin and eosin. Medium power, reduced ⅙.)



A. *B.*

Fig. 9 (Case 2).—*A*, Same section as Fig. 8, *A*. (Wilder's stain. High power, reduced ⅓.) *B*, Same section as Fig. 8, *B*. Previously nonapparent blood vessels are readily visible. (Wilder's stain. High power, reduced ⅓.)



A. *B.*

Fig. 10 (Case 3).—*A* and *B*, Hemangiopericytoma. (*A*, Hematoxylin and eosin. *B*, Wilder's stain. High power, reduced ⅓.)

an operation was considered inadvisable. During her final admission vaginal myomectomy was performed for a "myoma" protruding from the cervical os. Bleeding recurred 14 months later, and examination revealed a severely cachectic patient with an enlarged uterus and ascites, complaining chiefly of bone pain. She died 1½ years after "myomectomy." Autopsy was not performed.

TABLE I. CLINICAL SUMMARY OF CASES OF HEMANGIOPERICYTOMA OF THE UTERUS

CASE NUMBER	AGE (YEARS)	PARITY	SITE	OPERATION	FOLLOW-UP STATUS	FOLLOW-UP YEARS	REMARKS
1 A	25	0	Intramural	Myomectomy			Recurrence, 6 months later
B	28	0	Intramural	Hysterectomy	Living and well	8	Postoperative x-ray therapy
2	77	3	Submucous	Vaginal myomectomy	Dead	1½	Curettage performed 2 years and 3 years before myomectomy; tumor not revealed. X-ray therapy failed to control postmenopausal bleeding
3	71	1	Submucous	Hysterectomy	Living and well	6	Radium insertion 2 years before hysterectomy for "endometrial polyps." Postoperative x-ray therapy
4	43	1	Submucous	Hysterectomy	Living and well	11	Nests of tumor cells within lymphatics. Postoperative x-ray therapy

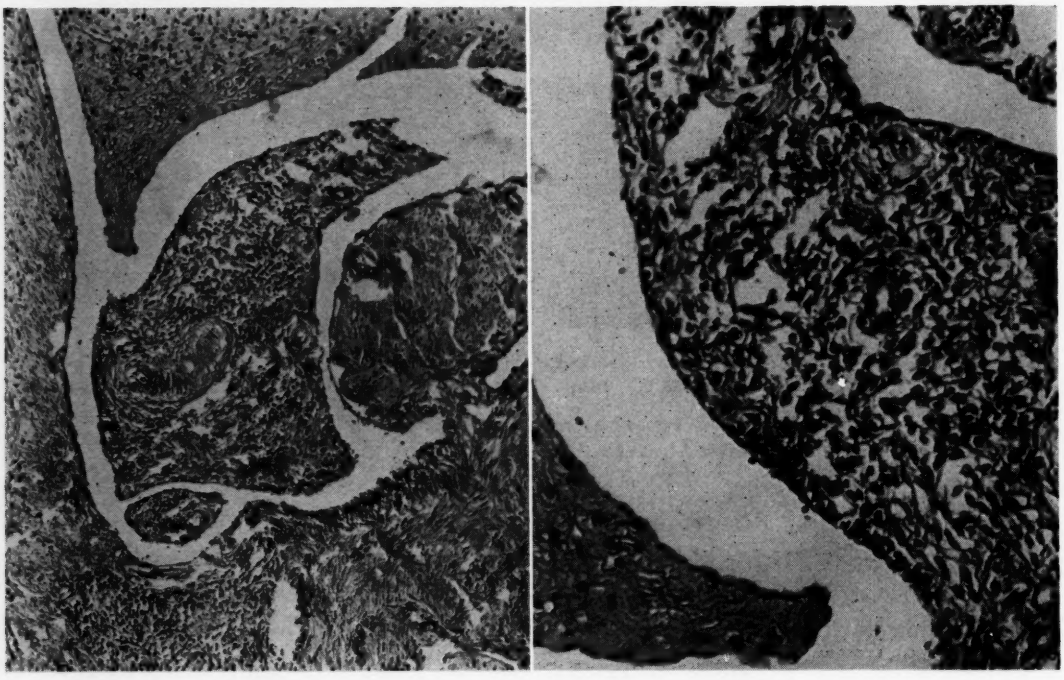
Comment

Since the first description of hemangiopericytoma, in 1942, Stout[5] has collected 144 cases, of which only 9 were uterine. All of the uterine hemangiopericytomas were benign. We have reported 4 more cases of hemangiopericytoma of the uterus, one of which was definitely malignant, and another that exhibited local aggression by recurring 6 months after the initial removal of the tumor.

The incidence of malignancy of hemangiopericytoma has not been definitely determined. Of the 144 cases reported up to May, 1953, approximately 79 per cent were benign and 21 per cent were malignant, on the basis of either metastases or local aggression. Those cases that revealed local aggression or recurrence, however, ran a benign clinical course, so that the recurrence may have merely been indicative of incomplete removal of the original growth. Therefore, unless metastases are present, the benign or malignant nature of a hemangiopericytoma cannot be determined histologically. Hyperchromatosis, increased mitoses, and the presence of nests of tumor cells within lymphatics do not necessarily presage a malignant clinical course. In the fatal case of our series these criteria of malignancy were absent. Case 4 is alive and well eleven years after hysterectomy, despite the finding of free tumor cells within the lymphatics of the tumor (Fig. 11, *A* and *B*).

Increased cellularity and morphologic variations of pericytes in different sections of the same neoplasm have led, in the past, to a diagnosis of sarcoma.

Since total hysterectomy is the treatment for symptomatic tumors of the uterus when the patient is at or beyond the menopause, discovery of a benign hemangiopericytoma rather than an apparent sarcoma is important solely from the point of view of prognosis and further therapy. In the younger woman in whom myomectomy is preferable, the true nature of these neoplasms should be determined. Further surgical treatment is indicated if sarcoma is the final diagnosis. During enucleation of these growths wide excision is advisable, because approximately one-fifth of all reported cases have had local recurrence.



A. *B.*

Fig 11 (Case 4).—*A*, Nest of tumor cells within lymphatic channel. (Hematoxylin and eosin. Medium power, reduced ⅙.)

B, New capillary formation in nest of free tumor cells. (Hematoxylin and eosin. High power, reduced ⅙.)

In the mistaken belief that these tumors were sarcomas, radiation therapy was given to all patients of this series. Case 2 was treated for a period of more than 3 years for postmenopausal bleeding with little appreciable effect upon the tumor.

Upon resurvey, 10 per cent of neoplasms previously classified as sarcomas, in the laboratory of the Jewish Hospital, have proved to be hemangiopericytomas, thus pointing up the importance of differential staining of all sarcomas.

Stromal Myosis and Hemangiopericytoma of the Uterus—Are They Identical Tumors?—During the present investigation and study of vascular tumors of the uterus it soon became apparent that hemangiopericytomas had been re-

ported previously under many different names, including "stromatous endometriosis,"[6] "perithelioma,"[7] "fibromyosis,"[8] "endometrioma" or "endometriosis interstitiale,"[9, 10, 11] "stromal" or "stromatous endometriosis,"[12, 13] and "endolymphatic stromal myosis."[14] When microscopic sections of the tumors herein reported, which fulfilled Stout's criteria for hemangiopericytoma, were submitted to other pathologists, the diagnosis made by many was "stromal myosis." Greene[15] has had a similar experience, for two of his cases of hemangiopericytoma of the uterus had previously been designated "stromal myosis," and one was used as an illustration of the latter entity in a standard textbook of gynecology.[16] This confusion prompted us to review all reported cases of "stromal myosis," and it seems likely that this entity and hemangiopericytoma of the uterus are identical tumors.

"Stromal myosis," an uncommon type of uterine neoplasm, is characterized by a proliferative invasion of the myometrium by cells morphologically resembling those of the endometrial stroma. An interpretive formulation of three groups of tumors of this general type was evolved by Novak.[17] Those in the simplest group are similar to adenomyosis, except for the absence of endometrial glands. A second more complex group is characterized by extensive endolymphatic invasion and extravascular penetration of tumor tissue, frequently wormlike in appearance. The third group is very similar to sarcoma in that the invading cells exhibit marked anaplastic activity.

The entity was first described by Doran and Lockyer[7] in 1909. They believed that the tumor cells originated in the endothelium of the perivascular lymphatics. In 1920, Casler[18] suggested a stromal-cell origin of the tumor, a view that has become rather widely accepted. Thus, it is generally believed that "stromal myosis" is a variant of adenomyosis, but without endometrial glands.[12] The recently described typical basket-weave reticular pattern of the neoplasm, being similar to that of the normal endometrium, was utilized to confirm an endometrial rather than a myometrial origin for the tumor. This reticular pattern, however, may also be present in other mesodermal tumors and is not peculiar to the endometrium.

Although the majority of specimens of "stromal myosis" exhibited a marked vascular appearance the possibility of a vascular origin, rather than stromal, had not been considered since the original report of Doran and Lockyer.[7] Reticulum stains that would reveal the occult vascularity of hemangiopericytoma would also reveal that of "stromal myosis." In both tumors there is an invasion of endothelium-lined spaces by free tumor-cell masses, and the cyto-architecture of "stromal myosis" is identical with that of hemangiopericytoma, as originally described by Stout and Murray.[1] Furthermore, cellular variations exhibited by "stromal myosis" have also been noted in pericytes. Despite a rather extensive experience with "stromal myosis," Frank,[19] as recently as 1944, did not believe that the constituent cells of the tumor were characteristic of either endothelium or stroma.

Stromal cells and pericytes are both mesenchymal in origin, and cells derived from this tissue may be markedly similar in appearance. Thus it may

be exceedingly difficult to differentiate fibroblasts, stromal cells, pericytes, smooth-muscle cells, and endothelial cells without special stains; differentiation of immature forms may be impossible. Therefore, the resemblance of pericytes and stromal cells is not surprising. In addition, if the cells of "stromal myosis" were stromal in origin, it might be expected in some instances that a functional response to the secretory hormone would have been noted.

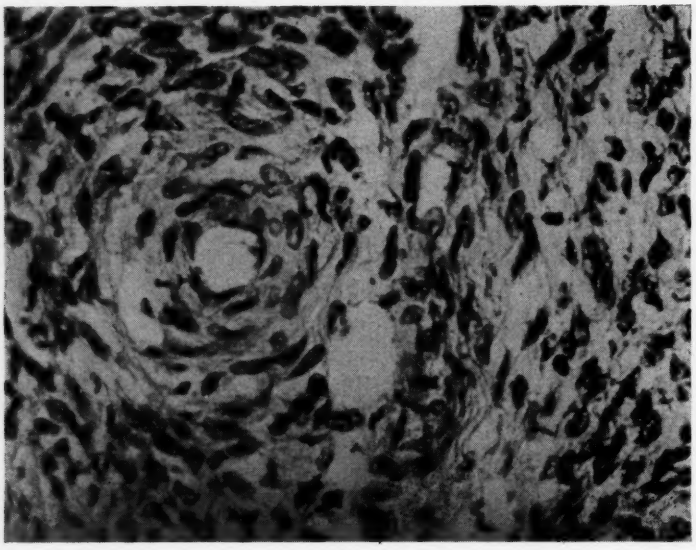


Fig. 12.—"Thick-walled" blood vessels that actually are capillaries. The thickness is caused by condensation of collagenous fibers; no smooth muscle demonstrable. (Hematoxylin and eosin. High power, reduced ¼.)

The rich vascularity of "stromal myosis" has been remarked by many investigators. Its striking feature was the presence of "thick-walled" blood vessels in addition to innumerable capillaries. Some of the "thick-walled" vessels are arterioles normally present in myometrium but which have become surrounded by invading tumor cells. The majority of these "thick-walled" vessels, however, were thought to be an integral component of the neoplasm itself, representing arterioles of small caliber. Similar vessels are also present in hemangiopericytoma, but when stained with Masson's and Wilder's differential stains they are seen to be capillaries with periadventitial condensation of collagenous and argyrophilic fibers in addition to a cuff of pericytes. The only investigator to publish results of differential staining of the "thick-walled" vessels of "stromal myosis" was Hill.[20] He noted also that these vessels were true capillaries, and that the thick walls consisted merely of condensed connective tissue and concentrically arranged "stromal cells." Although smooth-muscle fibers were not observed in these vessel walls, Hill did demonstrate that such fibers were present in the arterioles normally found within the myometrium. It thus appears likely that the "thick-walled" vessels characteristic of "stromal myosis" are identical with those present in hemangiopericytoma, whether of the uterus or of any other organ of the body.

Except for the absence of glandular elements, it has been suggested that "stromal myosis" is a variant of adenomyosis.[12] It is difficult to accept this concept for the following reasons: (1) The neoplasm occasionally develops postmenopausally, in women who are known to have an atrophic endometrium. (2) Adenomyosis rarely undergoes malignant degeneration as compared to the greater frequency of such change for "stromal myosis." Only 27 cases of malignant adenomyosis have been reported through 1938, and 7 of these were sarcoma. In each case endometrial glands were present. (3) If "stromal

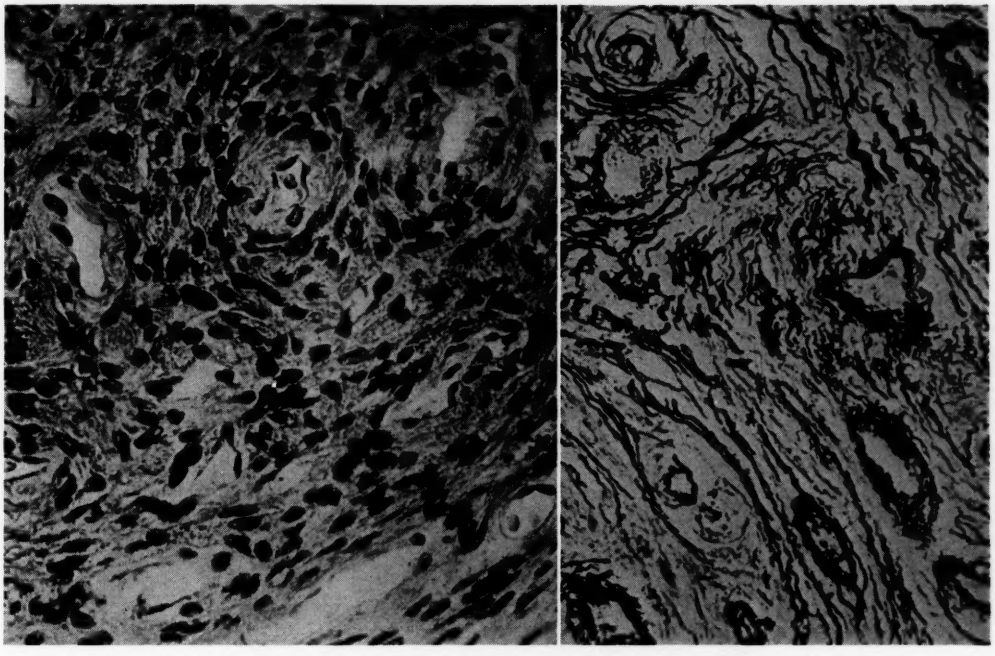


Fig. 13.—Hemangiopericytoma of neck. Compare with Fig. 14. (Reprinted by courtesy of Dr. A. P. Stout: Cancer 2: 1027, 1949.)

myosis" were similar to adenomyosis, recurrence of the tumor following castration should not be expected, unless an extraovarian source of estrogen is postulated. (4) The incidence of adenomyosis reported by most laboratories approximates 25 per cent, or more.[21] Of the 43 cases of "stromal myosis" reviewed by Park,[22] only 4, or 9.3 per cent, were associated with adenomyosis. Thus, the infrequent coexistence of these two conditions suggests that "stromal myosis" is not adenomyosis without glands.

Recurrence of a neoplasm, or metastasis, may often furnish information in regard to the origin of the tumor, because of the tendency to reproduce its original basic pattern. In all reported cases of recurrence or metastasis of "stromal myosis," regardless of the interval of time since excision of the primary tumor, the cyto-architecture of the original growth was reproduced. Frank[19] reported a recurrence 17 years after total hysterectomy for "stromal myosis," in which the identical pattern of the primary tumor was reproduced, suggesting an origin from vasoformative cells capable of blood-vessel formation, rather than from stromal cells.

The blood supply of "stromal myosis" is derived from an ingrowth of the normal blood vessels of the endometrium, and it is carried along with the tumor as it enlarges. Severance of this blood supply would obviously result in necrosis of the extended tumor, unless secondary vascular attachments had been established. A late recurrence after hysterectomy could not get a vascular supply from the endometrium, nor would one expect that the vascular pattern of the original neoplasm be reproduced. That this does occur suggests an origin from vasoformative tissue, such as pericytes, rather than from endometrial blood vessels or stromal cells. While Hill[20] and Embrey[6] both believe that stromal cells are capable of forming blood vessels, there is no evidence that a mature stromal cell can do so. The periodic regeneration of endometrial vessels is the result of outgrowth from pre-existing vessels.

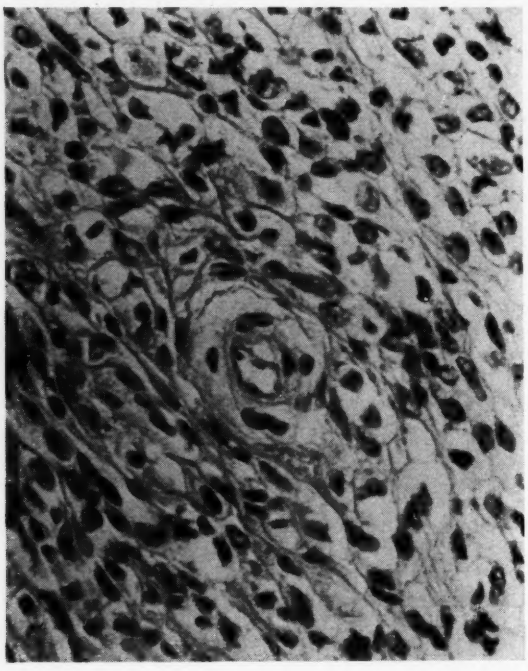


Fig. 14.—Hemangiopericytoma of the uterus. Compare with preceeding figure. (Hematoxylin and eosin. Medium power, reduced ¼.)

Critical review of previously reported cases of "stromal myosis" would probably substantiate the view that it has a vascular origin. Since similar tumors in other organs of the body are known as hemangiopericytoma, it appears reasonable to designate the identical neoplasm in the uterus by the same name (Figs. 13 and 14).

Summary and Conclusions

1. A review of tumors of the uterus previously reported as hemangioendothelioma and sarcoma has revealed that four of them were hemangiopericytomas.

2. The only presenting symptom common to the four cases was vaginal bleeding. This was probably due to the proximity of the neoplasms to the endometrial cavity.

3. Recurrence of the tumor was noted in two of the cases, one with invasion, and the other with metastasis. These were the only evidences of malignancy observed.

4. Except for metastases, the benign or malignant character of the neoplasm can be determined only by its future clinical course.

5. The basically vascular cyto-architecture of hemangiopericytoma can be demonstrated only by the utilization of differential stains. Silver stains demonstrate not only fine reticulum sheaths of capillaries, but also reveal occult and compressed vessels.

6. Although hemangiopericytoma is a rare tumor, differential staining of all vascular neoplasms would undoubtedly increase the number of such tumors detected.

7. Tumors of the uterus, previously reported as "stromal myosis," are probably identical with hemangiopericytoma and should be so designated.

We wish to express our appreciation to Dr. Arthur Purdy Stout, who so graciously reviewed this material.

References

1. Stout, A. P., and Murray, M. R.: Ann. Surg. **116**: 26, 1942.
2. Zimmermann, K. W.: Ztschr. f. Anat. u. Entwicklungsgesch. **68**: 29, 1903.
3. Fisher, E. R., Kaufman, N., and Mason, E. J.: Am. J. Path. **28**: 653, 1952.
4. Murray, M. R., and Stout, A. P.: Am. J. Path. **18**: 183, 1942.
5. Stout, A. P.: Personal communication.
6. Embrey, M. P.: J. Obst. & Gynaec. Brit. Emp. **59**: 846, 1952.
7. Doran, A. H. G., and Lockyer, C.: Proc. Roy. Soc. Med. (Obst. & Gynaec. Section) **2**: 25, 1909.
8. Frank, R. T.: Am. J. Cancer **16**: 1326, 1932.
9. Goodall, J. R.: J. Obst. & Gynaec. Brit. Emp. **47**: 13, 1940.
10. Miller, J. R., and Tennant, R.: Am. J. Obst. & Gynec. **47**: 784, 1944.
11. De Carle, D. W.: West. J. Surg. **53**: 48, 1945.
12. Robertson, T. D., Hunter, W. C., Larson, C. P., and Snyder, G. A. C.: Am. J. Clin. Path. **12**: 1, 1942.
13. Goodall, J. R.: A Study of Endometriosis, Endosalpingosis, Endocervicosis, and Peritoneo-ovarian Sclerosis, ed. 2, Philadelphia, 1943, J. B. Lippincott Company.
14. Henderson, D. N.: Am. J. Obst. & Gynec. **52**: 1000, 1946.
15. Greene, R. R.: Personal communication.
16. Curtis, A. H.: Textbook of Gynecology, ed. 5, Philadelphia, 1946, W. B. Saunders Company, pp. 340-341.
17. Novak, E.: Personal communication.
18. Casler, De W.: Surg., Gynec. & Obst. **31**: 150, 1920.
19. Frank, R. T.: Discussion of paper by Miller and Tennant.[10]
20. Hill, J. H.: Arch. Path. **43**: 527, 1947.
21. Hunter, W. C., Smith, L. L., and Reimer, W. C.: Am. J. Obst. & Gynec. **53**: 663, 1947.
22. Park, W. W.: J. Obst. & Gynaec. Brit. Emp. **56**: 759, 1949.

9 Prospect Park West (Dr. Pedowitz)
524 North Ave. (Dr. Felmus)
555 Prospect Place (Dr. Grayzell)

ROUTINE ANTEPARTUM ROENTGEN PELVIMETRY IN PRIMIGRAVIDAS

A. Marck, M.D., and A. Melamed, M.D., Milwaukee, Wis.

(From the Department of Radiology, Evangelical Deaconess Hospital)

ROENTGEN pelvimetry is currently employed to supplement clinical methods for the solution of obstetrical problems. The acceptance of this roentgen technique is based upon the results of numerous correlative clinical studies.[1, 2, 3] The advantages of roentgen pelvimetry in providing pertinent information not readily available by clinical observation or testing have been repeatedly substantiated. The question has been raised on occasion as to the value of routine roentgen pelvimetry of primigravidas during the late antepartum period. This type of examination would exclude consideration of such clinical factors as quality of forces of labor, moldability of the fetal head, status of the maternal soft parts, etc., in evaluating obstetrical prognosis. Under these conditions it has not been clarified as to whether antepartum roentgen pelvimetry contributes toward a decrease in fetal or maternal mortality, and favors greater competency in obstetrical practice.

An opportunity to pursue this type of study has been available to us during the past several years. With the cooperation of several of the attending physicians of the staff of the Evangelical Deaconess Hospital in Milwaukee, Wis., we have examined primigravid patients during the seventh and eighth months of gestation. Although the choice of methods of management and the final determination of prognosis rested on clinical grounds, it was felt that this series would serve as a test of the accuracy of roentgen pelvimetry in identifying problem patients and assisting in their care. Correlation of the results of these antepartum examinations with the outcome of labor was to follow the assembling of an adequate number of primigravidas.

Method

The Colcher-Sussman[4] radiographic technique with the addition of a semirecumbent view of the pelvic inlet was used for pelvic mensuration and description. Pelvic dimensions were reported as *small, intermediate,* or *large.* Statistical studies[5] invalidate sharply defined boundaries between ample, borderline, and inadequate pelves. It is also evident that small errors in measurement are well within the tolerance of obstetrical limitations. Critical dimensions, therefore, have been set aside in favor of *zones of pelvic capacity*[6] (Table I). Pelves were further analyzed with respect to basic architectural type as gynecoid, anthropoid, platypelloid, or android. An obstetrical prognosis was established in each instance using the schema of Table II. The theoretical effects of untoward measurements or structural variations were also noted.

TABLE I. ZONES OF PELVIC CAPACITY

DIAMETERS	SMALL	AMPLE
Pelvic Inlet.—		
AP	Below 11.1 cm.	Above 12.2 cm.
Transverse	12.6	13.5
Sum	23.6	25.6
Product	140	160
Midpelvis.—		
AP	11.5	12.5
Interspinous	10.0	10.7
Sum	21.0	23.2
Product	115	132
Pelvic Outlet.—		
Postsagittal	7.0	8.0
Intertuberosity	10.0	10.6
Sum	17.0	18.6

TABLE II. SCHEMA FOR ROENTGEN PROGNOSIS

PELVIC MENSURATION	ARCHITECTURE	PROGNOSIS
Ample	Gynecoid or anthropoid	Good
	Platypelloid	Guarded
Intermediate	Deviations in gynecoid and anthropoid pelves	Guarded
	Android	Guarded
	Minor variations in platypelloid pelves	Poor
Small	Android	Poor
	Mixed types with abnormal sacra	Poor

Comment

Three hundred eight patients in all were examined (Table III). Eight of this group are excluded because of placenta previa, premature separation of the placenta, toxemia, etc., which required operative procedures for purposes other than abnormalities in dimensions, structure, or mechanism of labor. Two hundred sixty-six mothers had spontaneous deliveries. Among these there was no maternal morbidity or death. Four stillbirths and 1 neonatal death, however, occurred. There were 34 instances (11 per cent) of complicated deliveries. In 27 of these, the solution to problems in mechanism of labor was obtained through major forceps procedures. Disproportion which occurred in 7 patients was treated by cesarean section. These operative procedures were not accompanied by any fetal or maternal deaths.

TABLE III. RESULTS OF ROUTINE ROENTGEN ANTEPARTUM PELVIMETRY STUDIES

PROGNOSIS	TOTAL CASES	SPONTANEOUS DELIVERY	OPERATIVE INTERVENTION	PROBLEMS IN MECHANISM OF LABOR	DISPROPORTION	STILLBIRTH	FETAL DEATH
Good	246	229	17 (7%)	17	0	3	0
Guarded	52	37	15 (29%)	9	6	1	1
Poor	2	0	2	1	1	0	0
Excluded	8						
	308	266	34 (11%)	27	7	4	1

Two Hundred forty-six mothers were classified in the "good" prognosis group; 229 of these had spontaneous normal deliveries. Seventeen mothers (7

per cent) of the "good" prognosis group, however, required major forceps procedures to accomplish delivery. These were not anticipated in the face of adequate pelvic capacity and favorable architectural features. Pelvic measurements and structural characteristics when interpreted independently of clinical factors measurable only with the onset of labor thus fail to identify a significant number of patients in whom operative intervention is eventually necessary for completion of delivery. Until this was sufficiently appreciated, there was a tendency on the part of the attending physicians to develop a false sense of security which caused delay in the application of proper corrective procedures.

Adequacy of pelvic dimensions in the "good" prognosis group of mothers is confirmed by the exclusive use of forceps procedures for the solution of various problems of descent and rotation. Three stillbirths occurred in the "good" prognosis mothers who had spontaneous deliveries. These fetal losses are apparently unrelated to maternal pelvic architectural or dimensional factors. In one instance, a macerated fetus indicated intrauterine death prior to the onset of labor. In the other 2, the cause of death was judged to be compression of the umbilical cord.

There were 52 patients in the "guarded" prognosis group. It was anticipated that the value of routine antepartum roentgen pelvimetry would be tested mainly by these patients. If the selection was correct, the attending physicians might then be forewarned and thus be able to choose the most advantageous method for the accomplishment of delivery, perhaps under slightly less urgent circumstances than is the rule. Thirty-seven mothers of this group experienced spontaneous uncomplicated labors, except for the use of outlet forceps. Only 15 mothers (29 per cent) of the "guarded" prognosis group required operative intervention for the completion of delivery. Roentgen pelvimetry during the antepartum period thus tends to be too inclusive in the "guarded" prognosis group. Possible complication is inferred in more primigravidas than actually demonstrate an abnormality in the mechanisms of labor or in fetal-pelvic relationships.

It has been suggested by others that antepartum identification by roentgen methods of the patients with "guarded" prognosis might result in a reduction of maternal or fetal morbidity or mortality. This contention is difficult to evaluate in our studies, particularly when the basic determinants for decisions regarding time and type of intervention depended upon clinical factors. One stillbirth and 1 neonatal death, both due to intracranial injury, occurred among the mothers of this group who delivered spontaneously. These losses might therefore suggest an error in equating "trial of labor" against unfavorable roentgen evidence. Although the low rate of fetal complications in this series is well within current standards of acceptable obstetrical practice, the possibility of further reduction through the use of roentgen pelvimetry cannot be controverted.

Six mothers in the "guarded" prognosis group were considered to present cephalopelvic disproportion as determined by clinical standards and demon-

strated by failure of the fetal head to descend or engage in the face of *intermediate* or *small* pelvic dimensions. These were treated by cesarean section. Review of the sequence of clinical events indicated early recognition of the need for this type of intervention. Apparently it would not have been delayed or missed without roentgen studies. Further analysis of "cephalopelvic disproportion" is not feasible because of lack of clarity in clinical terminology. The distinction between an obstructive labor due to bony relationships of fetus and maternal pelvis, and the failure of the fetal head to descend secondary to inadequate forces or untoward behavior of the soft parts is not always clear. The frequency of cesarean section in our patients, however, is no higher than in other series.

Two patients were placed in the "poor" prognosis group. The outcome here parallels that of the "guarded" prognosis patients. It is of interest that the occurrence of disproportion of skeletal origin is rather infrequent in our studies (2.3 per cent) and in those of others.

An incidence of only 17 operative cases among 54 mothers placed in the "guarded" and "poor" prognosis classifications is inconclusive for a convincing demonstration of the success of antepartum roentgen pelvimetry in pointing out the potential problem patient. Evidently the method of reporting and the determination of obstetrical prognosis tended toward undue conservatism. Likewise, the use of mensuration and architecture to the exclusion of associated clinical factors weighted the prognosis in an unfavorable direction.

Conclusions

Routine screening of primigravidas by roentgen pelvimetry in the antepartum period is not essential for the management of these patients. Without integration with the clinical features of labor, roentgen pelvimetry may prove misleading in the determination of obstetrical prognosis and choice of operative measures when such are indicated.

References

1. Savage, J. E.: Am. J. Obst. & Gynec. 61: 809, 1951.
2. Ane, J. N.: New Orleans M. & S. J. 98: 497, 1946.
3. Dyer, I.: Am. J. Obst. & Gynec. 60: 302, 1950.
4. Colcher, A. E., and Sussman, W.: Am. J. Roentgenol. 51: 207, 1944.
5. Hodges, P. C., and Nichols, R. L.: Radiology 57: 661, 1951.
6. Snow, William: Roentgenology in Obstetrics and Gynecology, Springfield, Ill., 1952, Charles C Thomas.

1821 West Wisconsin Avenue

A DECADE OF REPORTS ON TUBAL PREGNANCIES CONDENSED FROM THE LITERATURE PLUS THREE HUNDRED CONSECUTIVE CASES WITHOUT A DEATH

E. Crawford M.D., and H. Hutchinson, M.D.,* Shreveport, La.

(From the Department of Obstetrics and Gynecology, Highland Sanitarium and Charity Hospital, Shreveport)

THE practice of medicine is an art rather than a science because of its lack of constants. While many pathological processes present a high percentage of variables, only a few have a greater disparity of symptoms, signs, opinions and reports than ectopic pregnancy. It is this inconsistency that makes ectopic pregnancy so fascinating to study and, at times, so difficult to diagnose. We found in our series that only 7 per cent of the cases of tubal pregnancy followed a textbook pattern. Certainly most diseases present a more routinely typical picture than that.

In the various reports on ectopic pregnancy that have been published in the past ten years many discrepancies have been noted. One wonders just how great these differences actually are. With this query in mind we have condensed most of the literature of the past decade. Naturally enough, we have been curious to find how our own statistics compare. For this reason we have inserted throughout this paper our results in three hundred consecutive surgical cases of tubal pregnancy occurring between Jan. 1, 1943, through Dec. 31, 1952. It was discovered during this study that no deaths occurred in the series during the decade under discussion. The majority of cases were treated at the Shreveport Charity Hospital while the remainder were treated in a private institution. Abdominal pregnancies have been excluded since they are of sufficient interest to warrant a separate examination later.

We wish to emphasize that while this paper will list differences in the reports studied, we have no intention of theorizing as to their cause. To be sure, some of these differences will be unimportant, some are only apparent rather than actual, and an unfortunate few will be due to our inability to interpret correctly some authors' facts. Any discrepancy due to this human factor is obviously unintentional and represents one of the risks inherent in condensing material of this type.

Incidence

Schumann's figure for the incidence of ectopic pregnancy has been widely quoted. He reported one ectopic pregnancy for 303 deliveries, or 0.33 per cent. Other reports vary upward from 0.5 per cent,[14] 0.59 per cent,[20] 0.6 per cent,[37] 0.75 per cent,[9, 11] 0.77 per cent,[5] to 0.79 per cent.[2] Beacham[3] felt that an in-

*Present address, Medical Associates Bldg., 1930 Corlies Ave., Neptune, N. J.

cidence of 0.95 per cent "begins to approach the true incidence of ectopic cyesis to term intrauterine gestation."

Our study covers 31,712 live births and 300 consecutive ectopic pregnancies in that same period of time. This is an incidence of 0.95 per cent.

It will be noted that there is a variation in the literature of the decade from 1943 through 1952 of an incidence of 0.5 per cent to nearly twice that figure. This variation may be related to the increased incidence of pelvic inflammatory disease in large charity institutions through the country. As we will show later, 30 per cent of our cases had a pathological diagnosis of salpingitis. Or this variation may be related to the fact that the use of antibiotics in treating acute salpingitis has resulted in diseased tubes which remain patent. Prior to the use of antibiotics, pelvic infection more commonly caused complete closure of both tubes.

Seasonal Variation

MacFarlane and Sparling[27] noted a higher incidence of ectopic pregnancy during the months of May, August, and November. They added that their findings agree with the generally recorded fertility curves in their region. Davis and Malloy[8] noted the greatest number of their cases in May, August, and February.

In this series 44 cases occurred in January, 37 in May, and 29 in April. A lower incidence was noted in the other months.

Although all these reports list May as having a high incidence, we can detect no definite seasonal variation in them.

Age

The youngest patient with a tubal pregnancy was noted in the report written by Carrabba and Silberblatt.[5] They found an age range of 13 to 42 years. Other reports varied upward from 15 to 48,[3] 16 to 42,[30] 16 to 43,[1] 17 to 42,[8] 17 to 43,[20] 18 to 40,[34] 19 to 45,[10] to 20-43 in Hu's[14] paper. We found a range in our series of 15 to 48 years of age. The youngest patient found then in all papers studied was 13 years and the oldest 48. This corresponds to a wide childbearing span of 35 years as one would expect.

Different age groups were noted in many of the reports, making satisfactory comparison difficult. There were three figures found for the 20- to 40-year group; these three agree well, showing 95 per cent,[32] 94 per cent,[15] and 91.6 per cent.[27] In our series 91 per cent of patients varied from 20 to 40 years of age. One can safely conclude that more than 9 out of 10 ectopic pregnancies occur in women between 20 and 40 years of age.

While some of the figures are in agreement for shorter spans, one finds 70 per cent from 20 to 30 years of age in one paper,[8] but only 48 per cent in the same age group in another.[32] We found 52 per cent to be from 21 to 30 years of age in our 300 cases which agrees fairly well with the lower figure; between the two extremes an unexplained difference of 22 per cent exists.

The group from 25 to 34 years was represented in 69 per cent of cases in one report,[14] but only 56 per cent were from 25 to 35 in another series.[27] In

our study we also found 56 per cent to be between 26 and 35 years of age. These three figures agree fairly well, indicating that over half of the cases of eccyesis occur in the 25- to 35-year age group.

The average age for all patients in these reports varies by several years. Johnson[15] noted an average age of 27 years; others[1, 10, 14, 34] have older averages ranging from 28 to 31 years. We found an average age of 29 years. Thus there is a variation of 4 years in the average age of patients in the reports reviewed. However, combining all the reports, the age of the average patient would be just under 30 years.

Parity

There was considerable variation in the percentage of nulligravidas reported. Hu[14] reported 13 per cent as never having been pregnant before. We agree by noting 14 per cent in our series to be nulligravidas. Others have noted 16 per cent,[1] 17 per cent,[3, 34] and 18 per cent.[9] MacFarlane and Sparling[27] reported 34 per cent as being nulligravid. This makes a variation from 13 per cent to 34 per cent. This difference of 21 per cent is difficult to explain.

As for previous pregnancies, Bates and Nabors[1] reported 72 per cent as being either gravida i, ii, or iii. Other reports noted were Beacham's,[3] 65 per cent, and Douglas and co-workers,[9] 67 per cent for this same group. This is close agreement and shows that about two-thirds of patients with eccyesis have been pregnant one, two, or three times previously.

While investigating the parity in our series of cases, we found that 49 per cent, or roughly half, were para i, ii, or iii, while 4 patients were para x or higher.

Thus, the majority of patients studied had been pregnant at least once before. High parity does not rule out a diagnosis of ectopic pregnancy.

Previous Surgery

Previous laparotomy has been accused of causing ectopic pregnancy. MacFarlane and Sparling[27] noted a history of lower abdominal laparotomy in 30.9 per cent of cases of ectopic pregnancy. Miller[20] quotes Giles as saying that "from a group of 125 cases, 24 per cent of women who became pregnant after conservative therapy of this type [for perisalpingitis] had extrauterine gestation." In this same paper Siegal is quoted as having found that 15 per cent of his patients ectopically pregnant became so after suspension of the uterus. In our series 15.3 per cent had a history of previous lower abdominal surgery. Priddle and associates[34] report that 10 per cent of their cases had previous laparotomy. Thus in these few reports there is a difference of over 20 per cent, one author claiming 10 per cent and another that over 30 per cent of cases had previous laparotomy.

Repeat Ectopic Pregnancy

There is also some variation in the literature concerning repeat ectopic pregnancy. Miller[20] recalled Smith's study of 1,608 cases operated upon by

members of the American Gynecological Society and found 58 repetitions, or 3.5 per cent to have had a second ectopic pregnancy. Miller, in the same paper, added 5 more cases from Touro in a series of 137 ectopic pregnancies, or 3.6 per cent. Other reports[4, 5, 10, 17, 34, 37] range from 3.5 per cent to 7 per cent, but the highest noted was Henderson and Bean's,[35] who reported 9 per cent of cases with repeat ectopic pregnancy.

We found 12 repeat ectopic pregnancies in our series, or 4 per cent. While there is only a difference of 5.5 per cent, the larger figure is for some reason almost three times the smaller.

Pain With Bleeding

Pain and bleeding are two of the most common complaints in patients with an ectopic pregnancy. Two authors[8, 30] have reported pain in 100 per cent of cases; others[4, 5, 14, 27, 29] have recorded nearly 100 per cent of patients complaining of pain. In our series 94 per cent of the patients presented themselves with pain as a predominant symptom. Others[1, 3, 15, 34] have found it less often, in 93.5 per cent, 88.1 per cent, 85 per cent, and 67 per cent, respectively. Certainly over two-thirds of patients with eccyesis will complain of pain.

Vaginal bleeding without pain was far less common, being noted in 8.9 per cent of Beacham's[3] study, 4.7 per cent of our cases, and only 3.3 per cent of Carrabba and Silberblatt's[5] cases.

As for other vaginal bleeding one finds a considerable variation in the reports. Torpin[29] found bleeding in 85 per cent of his series. This is the highest percentage we found in the literature, but some others agree with it. MacFarlane and Sparling[27] found dark, chocolate-colored vaginal bleeding at some time in 81.8 per cent of cases. This report is almost identical with another[20] in which 81 per cent of cases showed abnormal vaginal bleeding. Others[30, 31] noted 78 per cent with slight vaginal bleeding and also said, "slight vaginal bleeding or spotting was noted twice as often in patients with a pelvic mass as in those with an acute rupture of the ectopic."

Still other reports on this complaint[1, 4, 13, 14, 15] range from 75 per cent to 43.3 per cent. In our series abnormal vaginal bleeding was noted in 70 per cent of patients. Of the 210 patients in our series who bled, 83 per cent admitted their bleeding was scanty. Collins and associates[7] believe "the character of the bleeding, whether spotting, moderate or flooding, continuous or intermittent, was of no diagnostic significance."

In any event, this is a range from a low of 42.3 per cent to a high of twice that, or 85 per cent. This means that some find abnormal vaginal bleeding as a complaint in ectopic pregnancy twice as frequently as do others.

Duration of Amenorrhea

There are those[18] who believe that in over 90 per cent of cases there is a history of amenorrhea. Collins and others[7] remarked, "13 per cent of the cases observed by us in the years 1937-1946 showed no deviation from their usual menstrual cycle." Apparently we can infer that not over 87 per cent

of their patients did deviate somehow from their usual menstrual cycle. Priddle and associates[34] found 81 per cent with a history of amenorrhea. Langman and Goldblatt[16] found 18 per cent of patients admitted within 30 days from the last menstrual period. In our own series 75 per cent had amenorrhea with 36 per cent not having menstruated for one to two months.

Others[3, 5, 20, 31] found amenorrhea in more than half their cases. Henderson and Bean[35] noted a missed period "in slightly less than half the patients in this series."

Here, then, is a confusing range of slightly less than half to over 90 per cent of the patients who have some history of amenorrhea preceding their ectopic pregnancies.

Duration of Symptoms

It is difficult to analyze the reports on the time lost from the onset of symptoms until a diagnosis was made. We have taken the onset of pain as being the initial symptom in the majority of cases. Pain is the most universal complaint in eccyesis and lends itself to comparison more easily than abnormal menses, vertigo, or other symptoms.

Beacham[2] noted 8.8 per cent of his cases presented themselves for treatment within 12 hours after the onset of symptoms. We found 15 per cent presented themselves with complaints of less than 24 hours' duration. Others[4, 8] found 22.5 per cent and 40 per cent of patients were admitted in less than 24 hours from the onset of symptoms.

Davis and Malloy[8] had 2.5 per cent wait one day before presenting themselves for treatment while Beacham[2] had 12.3 per cent wait one day.

We found 23 per cent waited from one day to one week. Another[8] reported 10 per cent waited one week, and an identical number waited for two weeks before seeking attention. Still another[2] had 17.2 per cent wait one to two weeks and, finally, we found 44 per cent of our patients waited one week to one month before seeking medical aid.

The figures reported in the literature vary so widely that comparison is difficult. It appears that patients in some localities present themselves for treatment much more quickly than those from other parts of the country. Either that or the onset of symptoms has been recorded differently by various authors.

In many reports, delay in operation has been accused of being an important factor contributing to the mortality in ectopic pregnancy. Among those who feel that this is true is Collins.[6] He has found the interval of time from admission to operation in his hospital has steadily declined until between 1947 and 1948 some 60 per cent of cases were operated upon within three hours. MacFarlane and Sparling[27] claim that 32.7 per cent of their patients were operated upon within four hours of admission, 27.2 per cent received operative treatment within 24 hours, and 13.6 per cent before 48 hours had elapsed. In all, 73.5 per cent of these patients had surgical treatment within 48 hours after admission. Johnson[15] divided his cases into latent and manifest. He found an average time spent from admission to operating room of three

hours, thirty-five minutes in the manifest and three days in the latent cases. Averaging his figures, we found an over-all time of 1.18 days. It will be noted that these periods start at the time of admission and not at the time of onset of symptoms.

We have tried to find whether a delay from onset to diagnosis increased our morbidity. We termed a patient morbid when the temperature was 100.4° F. on any two days postoperatively or 101 on any day postoperatively exclusive of the first 24 hours. Of the 300 patients, 58 per cent were morbid by this standard. We found that of those cases in which there had been symptoms less than 24 hours, 54 per cent of patients were morbid; of those who complained from one day to one week, 62 per cent were morbid; from one week to one month, 61 per cent were morbid; and from one to two months, 57 per cent were morbid. In these four different periods of time, the morbidity figures are roughly the same. From this, it would appear that the length of time lost between the onset of symptoms and diagnosis was unimportant as far as the morbidity in this series was concerned.

Nausea and Vomiting

Nausea and vomiting have been discussed in the literature with considerable diversity of opinion regarding the importance and frequency of these symptoms. The highest figure found was that of Langman and Goldblatt[16] who found nausea in 52 per cent and vomiting in 45 per cent of patients. We found vomiting in 48 per cent, but nausea was recorded in only 29 per cent of our cases. Most figures range somewhat lower, the smallest noted being that of Priddle and collaborators[34] in which nausea and vomiting were found in 9 per cent. This variation from half in one series to less than one-tenth of cases in another seems rather extreme.

Hu[14] found nausea and vomiting in 50 per cent of cases of rupture and in 33 per cent of cases without rupture; 40 per cent had nausea or nausea and vomiting combined. Nausea and vomiting occurred in 37.5 per cent of patients in another report.[8] Somewhat lower was the incidence in the report of Henderson and Bean[35] in which they found 30 per cent of patients complaining of nausea, vomiting, and diarrhea. Another study[27] found 30 per cent had nausea and vomiting associated with pain. Bookrajian[4] noted 28 per cent of patients had gastrointestinal symptoms, and nausea and vomiting characteristic of pregnancy were seen in 13 per cent of cases.

In summary, from approximately half to less than one-fourth of patients suffering from tubal pregnancy will have nausea and vomiting.

Weakness and Syncope

The frequency of the complaint of weakness varied greatly. The highest figure we noted was weakness in 43 per cent,[16] while the lowest we saw was in Collins'[7] article in which he states that "3 per cent conceded weakness." Our figure of 29 per cent with weakness seems comparatively high while others[34] with a report of 4 per cent are in agreement with the lowest. There is a difference of 40 per cent here which is undeniably extreme.

Syncope, fainting, or collapse was noted by Henderson and Bean[35] in 60 per cent of their cases. Other authors have noted a feeling of faintness or syncope at the time of rupture in 40.8 per cent of cases[4] fainting in over 33 per cent of cases,[16] and fainting in about 25 per cent of cases.[5, 18] We found that 21 per cent of our patients fainted at some time during their illness. The lowest figure noted was fainting in 15 per cent of cases.[9] Between the two extremes exists a wide variation of 45 per cent. Again, we find the explanation obscure.

Physical Examination

There is close agreement on many of the physical findings noted in the reports. Other findings vary.

Abdominal tenderness was present in all of Davis and Malloy's[8] cases. Other reports varied from 92.8 per cent,[32] 91.2 per cent,[4] 91 per cent,[3] 88 per cent,[14] 81 per cent,[20] to one paper[16] which reported that 20 per cent had no abdominal tenderness. We found this symptom in 90.67 per cent of our cases. All these reports, then, note abdominal tenderness in 80 per cent or more of cases.

An abdominal mass was noted in 12.3 per cent of our 300 cases. Other reports range down to slightly less than 10 per cent, and one recorded 3.2 per cent.[4]

Rebound tenderness was found in 33.67 per cent of our cases. Others report as high as 44 per cent[4] and as low as 25 per cent.[14]

Abdominal distention was noted to occur as frequently as 41 per cent,[14] 33 per cent,[16] and 26.4 per cent.[5] We found spasm or rigidity present in 29.3 per cent of our cases.

Considerable variation was noted in the palpation of a pelvic mass. The highest figure noted was that reported by MacFarlane and Sparling[27] who found a palpable extrauterine mass in 93.6 per cent. The next highest figure was the report[16] of an adnexal mass in over 75 per cent of cases, with the additional information that the mass was nearly always tender. Others found a pelvic mass in 57.1 per cent[32] and 55 per cent[14] of cases. A lesser figure was 50 per cent of cases with no extrauterine mass,[35] and still lower was the report of an adnexal mass felt in 45.6 per cent[4] and 43.3 per cent.[3] We found an adnexal mass in 38.3 per cent of our cases. A pelvic mass was found in only 36 per cent of Priddle's[34] series. There is a variation here of over 50 per cent.

Adnexal tenderness was noted in 72 per cent of Bookrajian's[4] cases and in 69 per cent of Hu's.[14] We found only 40.3 per cent with this symptom in our own series. This is a variation of over 30 per cent.

The sign of tenderness of the cervix on manipulation also has not found universal agreement in the reports. Priddle and co-workers[34] felt this to be one of the chief findings. It was found in 80.3 per cent[3] of cases, 66 per cent,[16] 60 per cent,[32] and 56 per cent.[4] We found this symptom to be present in only 31.6 per cent of our cases which was the lowest figure reported. This is a variation of nearly 50 per cent in papers studied.

A soft cervix was found in 49 per cent of Word's[32] cases, 44 per cent,[4] 35.4 per cent,[27] 15 per cent,[8] and finally in 10 per cent.[14] We found a soft cervix in 18.67 per cent of our patients. These statistics represent a variation of 39 per cent. The highest figure is almost five times the lowest.

Uterine enlargement was found in 46.3 per cent,[27] 39.2 per cent,[4] 35 per cent,[35] 20 per cent,[14] and 12.5 per cent.[8] We found an enlarged uterus in 25 per cent of our cases.

A full, boggy, or doughy mass was found in the cul-de-sac in over 50 per cent in one study,[16] but in only 9 per cent in another.[14] We found this bogginess or fullness in 20.6 per cent and a definite mass in 11 per cent.

With variations in physical findings such as we have recorded, it is clear that even the best diagnosticians will occasionally misdiagnose ectopic pregnancy.

Laboratory Determinations

One would expect reasonable agreement in the laboratory findings that are felt to be of value in the diagnosis of ectopic pregnancy. That is not completely valid as will be shown.

A. Sedimentation Rate.—

The sedimentation rate is reported in some texts[41] to be accelerated in cases of internal hemorrhage, but to be unaffected by an unruptured ectopic pregnancy.

Henderson and Bean[35] found the sedimentation rate to be within normal limits in most cases. Douglas and others[9] feel the sedimentation rate is usually slow. We cannot agree completely. In our series we found only 12.5 per cent of 64 sedimentation rates were 10 mm. or less in 1 hour, 62 per cent were between 10 and 30 mm. in 1 hour, and 25 per cent over 30 mm. in an hour (Cutler microsedimentation rate in which 10 mm. per hour is considered normal for females). Hu[14] found 88 per cent of cases had a sedimentation rate of less than 30 mm. per hour which is in the same range as our figures. That is, there is moderate acceleration in the sedimentation rate in both reports.

On the other hand, Langman and Goldblatt[16] found a sedimentation rate of 60 minutes or over (Linzenmeier) in approximately two-thirds of cases. In less than 8 per cent of this series the sedimentation rate was under 30 minutes. They added, "It is important to note that where the sedimentation rate was 30 minutes or less, the diagnosis of ectopic pregnancy was usually not confirmed at operation." The normal values are from 200 to 600 minutes.[43] It would seem then that these sedimentation rates are rather rapid. Depending on the article read, sedimentation rates may be said to vary from slow to normal to moderate or fast.

There were a few comments gleaned from the literature which show the confusion that exists.

On one hand, Te Linde found the sedimentation rate of no value "as a differential test between inflammation and ectopic pregnancy."[38] But Johnson feels the sedimentation rate is helpful in differentiating between pelvic in-

flammation and ectopic pregnancy in latent cases. Others call it "more confusing than helpful,"[27] "not an important factor in arriving at a diagnosis,"[4] or just say it was of no help.[32]

We believe that where so much confusion exists over a test it generally indicates that the results are not diagnostically significant.

B. Urine Tests for Pregnancy.—

Beacham[3] did a Friedman-Lapham test in 28 cases of eccyesis and found a positive reaction in 22. This would indicate 79 per cent positive reactions. He feels, as does Te Linde,[38] that a positive report is of definite value. Bookrajian[4] used the Friedman test in 31 cases with 23 positive reports or 75 per cent. He feels the test is a valuable diagnostic aid in the nonurgent case. We had 21 positive Friedman tests and 7 negative reports, so that we found 75 per cent positive reactions, too. Others[9] also recommend the frog test, and the statement was made by one,[16] "that where the symptoms are not obvious and do not demand an immediate operation, the A-Z test is of the greatest aid in arriving at a diagnosis." On the other hand, there are those not quite so impressed with pregnancy tests. They hold such opinions[35] as, "the urine tests for pregnancy were of only minimal help in diagnosis"; another,[15] while discussing eccyesis, claims "the A-Z test is of little importance"; and another,[8] that "the Friedman test is not recommended as a diagnostic aid in ectopics."

C. Hemoglobin and Red Cell Count.—

The literature also contains some conflicts in numbers as well as in interpretation regarding the hemoglobin and red-cell counts in eccyesis.

One paper[8] reported a hemoglobin below 70 per cent in 38 per cent of cases, and another agrees that the hemoglobin is below 70 per cent in fewer than half of the cases.[35] One[27] reported the hemoglobin to be less than 60 per cent (Sahli) in 38 per cent of patients, and another found the hemoglobin to be less than 50 per cent in one-fifth of patients.[31] We found a hemoglobin of 55 per cent or more in 61 per cent of our cases (8.6 Gm. hemoglobin in our laboratory). Of the reports in our series 23 per cent were from 39 per cent to 54 per cent hemoglobin (6.1 to 8.5 Gm.). From these figures it is apparent that the majority of patients are anemic.

Some comments that we noted included the statement[12] that anemia is the rule. Others[31] feel the red-cell count increases more rapidly than the hemoglobin when hemorrhage is stopped; still others[15] are of the opinion that "the total cell count is the most important part of the blood picture in ectopic pregnancy." Several[13, 15, 27, 32] aver that repeated red-cell counts and hemoglobin determinations are important in the diagnosis of tubal pregnancy.

D. White-Cell Count.—

The white-cell count was also discussed by Beacham[3] and others,[27] who believe it is of little value in differentiating ectopic pregnancy from pelvic inflammatory disease. Davis and Malloy[8] found the white count comparatively low. Others[8, 27, 31] concluded that a white count of 10,000 divided their series into almost equal halves. Still others[35] reported the majority of white-cell counts were above 10,000, and one[4] found 70 per cent had a leukocytosis of

9,000 or over. We found a white-cell count of 10,000 or over in 90 per cent of our cases with 12 per cent over 20,000 in the 132 cases in which white-cell counts were recorded. The differential counts showed 80 per cent or more polymorphonuclear cells in 71 per cent of the reports from our laboratory. Most writers, then, report a leukocytosis in the majority of patients with tubal pregnancy.

These variations in laboratory reports have made us resort to fewer and fewer diagnostic laboratory procedures. As soon as the diagnosis of ectopic pregnancy is suspected in one of our cases, we routinely have blood typed and matched and the Rh factor determined immediately. Falls[12] agrees that typing of blood and Rh factor determinations should be carried out. Collins[7] states, "Laboratory procedures have not been of much aid to us in the diagnosis of oviducal pregnancy. The only laboratory tests of constant value are the blood type and the Rh factor determinations, and these are not diagnostic procedures."

Hemoperitoneum

Word[32] states that hemoperitoneum was found at laparatomy in 90.7 per cent of his cases. We found 88 per cent with blood in the peritoneal cavity at laparotomy in this series. Langman and Goldblatt[16] noted 500 c.c. or less of free blood in 35 per cent, 500 to 1,500 c.c. in 40 per cent, and over 1,500 c.c. in 14 per cent of their patients.

There were 96 cases in our series in which there was some estimation of the amount of blood found in the abdominal cavity at laparotomy. Of these, 47 per cent had less than 500 c.c., 27 per cent had 500 to 1,000 c.c., and 26 per cent had over 1,000 c.c. It can be seen in these reports that over 50 per cent of patients with hemoperitoneum lost over 500 c.c. of blood apiece.

Our estimates here are undoubtedly too low. We have noted elsewhere in this paper that 80 per cent of our patients were each transfused with an average of over 1,500 c.c. of whole blood.

Tube Involved

There have been various theories postulated to account for the predominance of right-sided over left-sided tubal pregnancies. It is not our purpose to consider possible causes, but to see how various reports compare.

Douglas[9] found the right tube involved in 64 per cent and the left in 36 per cent of cases. That figure represents the highest right-sided involvement noted in the decade under discussion. Hu[14] found the right tube involved in only 49 per cent and the left in 51 per cent, which is the only reversal of the right-sided dominance that we found. Others noted the right tube involved in 63.6 per cent,[27] 61 per cent,[32] 60.1 per cent,[3] 53.7 per cent,[29] 53 per cent,[34, 37] and 50 per cent.[4, 20]

We found 53 per cent of our 300 cases involved the right tube, 46 per cent the left, and 1 per cent were bilateral. That last figure represents 3 unusual cases in which pregnancies were found in both tubes simultaneously.

Site of Tubal Involvement

Beacham[3] records the ampulla as the tubal site most commonly involved. Others agree with this but in varying percentages. They range from 90.7 per cent,[32] 84.4 per cent,[29] over 66 per cent,[16] and 60.9 per cent.[27] The outer third of the tube was affected in 44 per cent of Priddle's cases.[34]

We followed the latter's example and divided the tube into thirds. Our investigation showed 46 per cent to be in the distal third, 39 per cent in the middle third, and 14 per cent in the proximal third.

An interstitial location was noted in 6.3 per cent of MacFarlane and Sparling's[27] cases, 3.9 per cent,[29] 2 per cent,[34] and 0.07 per cent of Word's[32] cases. We found two such cases in our series which is less than 1 per cent interstitial pregnancies.

Simultaneous Extrauterine and Intrauterine Pregnancy

In 1951 Sprague and Sprague[28] reviewed the literature and found 416 cases of this most interesting condition. Torpin[29] recorded two cases but, his report was published prior to Sprague's work and is probably included. Johnson[15] also recorded two cases of heterotopic pregnancy. DeVoe and Pratt[23] have added a case of term intra-extrauterine gestation which is rare indeed. The most recent report that we have reviewed is that of Zaron and Sy[40] in which they bring the total of cases found to 415.

We have six cases to add. The first occurred in 1946. The patient had an ectopic pregnancy in the right tube. At operation, a rupture was found in the isthmic portion of the tube. Four days postoperatively, this patient passed a 45 mm. fetus in an amniotic sac per vaginam with considerable cramping and blood loss. The second case is similar in that this patient also had a ruptured ectopic pregnancy in the isthmus of the right tube. Four days postoperatively, she passed a 5 cm. fetus with a placenta per vaginam. In neither of these cases have we been able to ascertain the fate of the umbilical cord, but we still feel both these cases should be considered simultaneous intra-extrauterine pregnancies.

Our third and fourth cases are similar. One patient had an ectopic pregnancy removed on Jan. 6, 1949. There was a rupture here also in the isthmic portion of the right tube. The opposite tube was ligated. On July 17, 1949, about six months later, she delivered a full-term infant here that weighed 6 pounds, 12 ounces. The fourth patient had an ectopic pregnancy here Jan. 31, 1952, at which time the right tube was removed. Less than seven months later on Aug. 27, 1952, this patient delivered a full-term infant here that weighed 7 pounds, 12 ounces. There can be no question of the validity of these last two cases being simultaneous intra-extrauterine pregnancies.

The fifth patient was delivered here July 13, 1951. She was sterilized post partum. In a portion of one of the tubes removed by a modified Pomeroy technique an old ectopic pregnancy was found. This was partly hyalinized and calcified, but represents an intra-extrauterine pregnancy.

The sixth case is not as clear-cut. The patient was operated upon here on Jan. 13, 1951, and an ectopic pregnancy removed. One month previously, she had had a dilatation and curettage in another hospital for an incomplete abortion. Their pathologist reported "bits of placental tissue" in the scrapings. Our pathologist has not reviewed the slides.

Previous Salpingitis

Johnson[15] found 51 per cent of his patients had salpingitis. Lower figures include one of over 50 per cent of cases with inflammatory changes both acute and chronic,[16] another of 36 per cent with salpingitis,[3] 28 per cent,[34] 27 per cent,[35] and 20 per cent.[27] One[14] reported evidence of infection in both tubes in 19 per cent of cases and infection in the involved side in 11 per cent. Carrbabba and Silberblatt[5] noted that 18 per cent of his cases had a history of salpingitis.

We have our pathologist's report of salpingitis in 89 cases, or 29.67 per cent of our ectopic pregnancies. Our pathologist, Dr. W. R. Mathews, also suspects there was a chorioma occurring in a tubal pregnancy in 1943. This patient never reported for follow-up Friedman tests, however, so we lack verification. Two choriocarcinomas in ectopic pregnancy occurring here prior to 1943 have already been reported.[39]

Surgery for the Ectopic Pregnancy

In most of the papers studied the point was made that a salpingectomy was the preferred treatment, but that some salpingo-oophorectomies were inevitable. Pleas were made to conserve the ovary when possible. Bookrajian[4] found a total of 96 per cent had either a salpingectomy or salpingo-oophorectomy in his series. Others noted 94 per cent,[27] 93 per cent,[35] 90 per cent,[34] and 81 per cent[2] of cases had one or the other operation.

In our series 51 per cent of the cases had a salpingectomy while 43 per cent had a salpingo-oophorectomy. This totals 94 per cent of patients handled by one operation or the other.

Hysterectomies were done on 17 per cent of one of Beacham's[2] series. This figure was reduced considerably in a later period.[3] We had an incidence of 5.3 per cent abdominal hysterectomies in our 300 cases.

Miller[20] feels that "no more surgery should be practiced upon the victim of a ruptured ectopic pregnancy than is absolutely necessary to ensure a primary postoperative recovery. He, who under such circumstances incidentally removes the 'chronic appendix' or suspends the uterus, or explores the abdomen after removing the affected tube, will increase his operative mortality by a great percentage." Others put it a bit differently by saying that surgical treatment should be limited to the primary condition,[27] or that additional elective surgery is very rarely warranted.[34]

On the other hand, Collins[6] noted that in his series there were 42 cases with incidental appendectomies and none of these died. In another series there were 22 appendectomies without postoperative complications.[35] Camp-

bell[37] found "those with incidental surgery did as well as a group as those treated with specific surgery." There were 61 incidental appendectomies in his study.

We have listed 29 incidental appendectomies without a mortality. This does not mean that we are recommending incidental surgery, but we doubt that additional surgery must always be deferred in carefully selected cases.

Preoperative Diagnosis

The highest percentage of correct preoperative diagnosis was that of Henderson and Bean[35] who made the incorrect preoperative diagnosis in only 10 per cent of cases. Langman and Goldblatt[16] noted 29.7 per cent incorrect diagnoses. Others varied, as 87.1 per cent,[32] 82 per cent,[3, 9] and 81 per cent[37] correct preoperative diagnosis. Our diagnosis was correct preoperatively in 84.3 per cent of cases.

Several authors found some sort of pelvic inflammation caused the most errors in diagnosis.[16, 32, 36] Beacham found myomas caused mistaken diagnoses most often, with pelvic inflammatory disease a close second.[3] Of our 47 ectopic pregnancies which had erroneous preoperative diagnosis, a tubo-ovarian abscess was found in 19 per cent and myomas in 15 per cent.

From this it can be seen that one or two out of every ten ectopic pregnancies will be misdiagnosed. Our impression originally was that this figure would be higher.

Blood Transfusion

Collins[6] found that 86 per cent of patients with an ectopic pregnancy were transfused in his series. For the 131 cases he found 260 pints of blood were used. This is an average of 990 c.c. per case, or 1,150 c.c. per patient transfused. Word[32] gave his 140 patients 136,000 c.c. or an average of 971 c.c. per patient. Beacham[3] noted that 250 patients received 239,100 c.c. or an average of 956 c.c. per case. We gave an average of 1,695 c.c. per patient transfused, or 1,345 c.c. average for all 300 cases.

Other reports showed: 60 patients given an average of 900 c.c. of blood preoperatively while 78 received an average of 670 c.c. during surgery[4]; and another, 116 cases of a series of 136 transfused or 85 per cent of cases[34]; 57 per cent[27]; 51 per cent[37]; and less than one-third received any blood at all.[16]

We have given 808 pints to 238 of our patients with ectopic pregnancies. This means that 79.3 per cent of patients each received an average of 1,695 c.c. of blood. We feel certain that our liberal use of blood transfusions has been an important factor in reducing the mortality from ectopic pregnancy.

Mortality Rate

Priddle and associates[34] had a mortality rate of 2.9 per cent. MacFarlane and Sparling[27] had 2.72 per cent, and Langman and Goldblatt[16] had a rate of 2.6 per cent. Torpin[29] says that the average United States mortality is probably 10 per cent, 3 per cent is good, and 1 per cent excellent. He lists

a rate of 2.5 per cent in his paper. Others had 2.4 per cent,[15] 2.3 per cent,[35] 1.6 per cent,[11] 1.36 per cent,[30] 1.3 per cent,[3, 5] 0.78 per cent,[9] 0.7 per cent,[32] and Campbell[37] had a mortality rate of 0.25 per cent.

Ours is the first series we found with a mortality rate of zero. We have not had a death in our entire series of 300 surgical cases of tubal pregnancy occurring consecutively from Jan. 1, 1943, until Dec. 31, 1952.

In the preceding decade there were eight deaths from ectopic pregnancy in Shreveport Charity Hospital; all eight deaths were proved by autopsy. One must wonder how many of these patients would have been saved had they developed their ectopic pregnancies today. Our modern blood banks, antibiotics, and residency training programs should certainly have saved most of them. Perhaps today's low mortality rate is also due to the fact that we are more "ectopic minded" now. If so, much of the credit must be given to Drs. Beacham and Collins, since the majority of our house staff are New Orleans trained.

Cul-de-sac Aspiration

Word[32] noted that "The most consistently positive diagnostic test was the cul-de-sac puncture." He found it to be 90 per cent accurate and added that "in five years of extensive employment of cul-de-sac aspiration by our house staff, there has been no sequela." Beacham[2] also advocates culdocentesis and noted in 1950 that it was done on 89 per cent of cases and allowed them to make an unequivocal diagnosis in all 89 per cent. Other comments were that the most valuable aids in diagnosis were posterior colpotomy and aspiration of the cul-de-sac[35]; "The value of cul-de-sac aspiration has long been established."[1] Collins[6] also feels that culdocentesis is worth-while and that it has reduced the total hospital time in his cases. Douglas and others[9] make the interesting observation that in all 24 cases misdiagnosed in their series not one had been investigated by cul-de-sac aspiration.

On the other hand, Davis and Malloy[8] did not use it, but feel it is a valuable diagnostic aid. Draa[10] said, "We do not believe that colpopuncture is of value in establishing the positive diagnosis of ectopic pregnancy." To this, Ware[30] still agrees and others add that the needling of the cul-de-sac "introduces infection into an otherwise clean case, outweighs the value of a procedure which is usually not necessary."[27]

We have done culdocentesis in 178 cases, or 59.34 per cent of our total. Of these, 92 patients, or 51.7 per cent, became morbid. Of the remaining 122 patients, who did not receive cul-de-sac aspiration, 63.1 per cent became morbid. From these figures one would infer that cul-de-sac aspiration in our hands has resulted in a lowered morbidity. This supports Collins'[6] opinion that culdocentesis lessens morbidity. We found blood in 90 per cent of our cases of ectopic pregnancy in which the procedure of cul-de-sac aspiration was attempted.

We have done numerous diagnostic cul-de-sac punctures, too, in which blood was not found, and the patient was permitted to go home. Rather than

doing many expensive and time-consuming laboratory procedures, we often resort to culdocentesis. It is our feeling that this procedure is a valuable diagnostic aid and does not increase the morbidity in ectopic pregnancy.

Morbidity

Draa[10] found that of his 224 patients, 112, or 50 per cent, were febrile. He showed in his series that removal of the ectopic pregnancy through a colpotomy incision produced the lowest morbidity rate. Others[27] found 23.7 per cent of their patients had "stormy" postoperative courses and 16.2 per cent were morbid.[37] Priddle and collaborators[34] had a low figure of 5.8 per cent morbidity by "usual standards."

Our morbidity rate was 55.67 per cent which is the highest rate we have noted. We termed a patient morbid if she developed a temperature over 100.4° F. on any two postoperative days, or over 101 on any one day postoperatively. Other morbidity rates may have been computed on a less stringent basis.

Shock

Bookrajian[4] noted a shock syndrome in 35.2 per cent of cases, while Draa[10] had only 8.9 per cent in shock at some time, or one-fourth as often. Other high figures noted were 33 per cent[34] in shock on admission, 30 per cent[35] and 29.9 per cent[20] in shock at time of operation. Lower figures were 18.5 per cent,[32] 13.6 per cent with signs of shock on admission and 6.8 per cent later,[3] 11 per cent in shock,[16] and deep shock in 10 per cent.[5] There is a difference of over 20 per cent between the two extreme figures.

Some signs of shock were noted in 70 of our cases, or 23.3 per cent. We further found that 60 per cent of those in shock became morbid postoperatively. This suggests that hemoperitoneum may be the cause of much of the morbidity in ectopic pregnancy.

Dilatation and Curettage

Romney, Hertig, and Reid[24] gathered 217 cases in 39.1 per cent of which decidua was found. Word[32] reports decidua found in 3 cases from 9 curettements, or 33 per cent with decidua.

We performed this operation 59 times, or 19.67 per cent of patients. Of those curetted, 27 per cent showed decidua, 43 per cent showed proliferation, and 25 per cent showed secretory endometrium.

It will be recalled that of the pregnancy tests reported, roughly three-fourths were positive. On the other hand, there was decidua found in the uterine scrapings from only about one-third or less of the cases noted here. Superficially, this might appear contradictory to some. For a simple, lucid explanation one should refer to Novak,[41] who has written a most interesting section on the histology of the endometrium in ectopic pregnancy. He explains how the death of the embryo, plus the passage of time, will give rise to other than decidual tissue. In 7 out of 21 cases where the uterus was available for study, he found definite decidual change. Novak states that at times

the microscopical examination of uterine curettings is invoked in the diagnosis of tubal pregnancy. While "often this is justifiable," he adds that "in a large proportion of cases, more particularly in those in which bleeding has been a symptom, little or no information of diagnostic value is to be looked for from the microscopical examination of the uterine scrapings."

One report[34] goes a step further and claims that a dilatation and curettage as an aid in diagnosis of ectopic pregnancy are of no benefit and useless.

Admission Temperature

Draa and Baum[10] noted that a low-grade temperature with a high white count was usually associated with profuse bleeding in the peritoneal cavity. Ware[31] feels that temperature readings are useful in the diagnosis of ectopic pregnancy. He found in his study that 96 per cent of his patients had a temperature below 101° F. and none were over 103. Others[27] found 80 per cent were not over 99.3°; 79 per cent were below 99.9°.[35] Beacham[3] noted 76 per cent of his patients had temperatures under 99° on admission.

Of our patients, 73 per cent had admission temperatures between 98 and 100°, 15 per cent above 100°, and 11 per cent below 98.° For this reason we have become reluctant to make a diagnosis of eccyesis if the patient's temperature is much over 100° F.

Length of Sterility

One study[34] found that 40 per cent of the patients had not been pregnant within the past five years. Another[27] stated that 48 per cent of cases had an absolute or a relative sterility. One[16] noted that five years or less had elapsed in more than one-third of cases, and still another[4] found 35.2 per cent of the patients had been pregnant within five years or less.

In this series 25.33 per cent of patients had been pregnant within six years and 13 per cent within one year.

We felt it would be interesting to see how many of our patients had become pregnant since their eccyesis. We have hospital records that show 26 patients have subsequently become pregnant or 8.67 per cent have had some treatment for pregnancy at our hospital since their ectopic pregnancies. Since midwives still flourish in parts of Louisiana, this figure is undoubtedly low.

Summary and Conclusions

Figures on ectopic pregnancy taken from reports published between 1943 and 1952 show many variations. While some differences must be anticipated in any medical study of this type, few would be expected to vary so widely.

We have compared them with our statistics from 300 consecutive cases of tubal pregnancy in the same decade. While most of our figures are in the same range as those of other reports, some of our results, e.g., morbidity, differ widely from the rest. This may be due to the strict criteria used by us to define morbidity.

Our object was not to explain these variations. We have contented ourselves with simply showing that these differences do exist and that they are

frequently large. Reasons for these discrepancies will have to be formulated by older and wiser heads. That these variations could help account for much of the difficulty in diagnosing ectopic pregnancy is obvious.

Our mortality rate of zero is gratifying. We have used blood transfusions more freely in our cases than was noted in any other series. That was probably the main factor in making our mortality rate the lowest reported. We optimistically feel that more reports of zero mortality in ectopic pregnancy are certain to be published soon.

References

1. Bates, C. R., and Nabors, G. C.: South. M. J. **45**: 240, 1952.
2. Beacham, W. D., et al.: J. Missouri M. A. **48**: 629, 1951.
3. Beacham, W. D., Collins, C. G., Thomas, E. P., and Beacham, D. W.: J. A. M. A. **136**: 365, 1948.
4. Bookrajian, L.: Am. J. Surg. **82**: 432, 1951.
5. Carrabba, S. R., and Silberblatt, W. B.: Am. J. Obst. & Gynec. **64**: 1154, 1952.
6. Collins, C. G., Beacham, W. D., and Beacham, D. W.: Am. J. Obst. & Gynec. **57**: 1144, 1949.
7. Collins, C. G., et al.: Chicago M. Soc. Bull. **54**: 357, 1951.
8. Davis, J. D., and Malloy, R. R.: J. Nat. M. A. **40**: 3, 1948.
9. Douglas, G. F., et al.: J. Internat. Coll. Surgeons **15**: 28, 1951.
10. Draa, C. G., and Baum, H. C.: Am. J. Obst. & Gynec. **61**: 300, 1951.
11. Anderson, G. W.: Am. J. Obst. & Gynec. **61**: 312, 1951.
12. Falls, F. H.: S. Clin. North America **30**: 207, 1950.
13. Gordon, C. A., et al.: Am. J. Surg. **82**: 485, 1951.
14. Hu, I. F.: Carle Hosp. Clin. Bull. **3**: 18, 1950.
15. Johnson, W. O.: Am. J. Obst. & Gynec. **64**: 1103, 1952.
16. Langman, L., and Goldblatt, M.: Surg., Gynec. & Obst. **69**: 65, 1939.
17. Lingenfelder, J.: U. S. Armed Forces M. J. **1**: 550, 1950.
18. MacFayden, E. H.: Canada M. A. J. **62**: 51, 1950.
19. McKenzie, C. H.: Minnesota Med. **33**: 1215, 1950.
20. Miller, H. E.: Am. J. Surg. **48**: 47, 1940.
21. Pisani, B. J.: Surg., Gynec. & Obst. **95**: 149, 1952.
22. Pratt, J. H.: S. Clin. North America **27**: 807, 1947.
23. DeVoe, R. W., and Pratt, J. H.: Am. J. Obst. & Gynec. **56**: 1119, 1948.
24. Romney, S. L., Hertig, A. T., and Reid, D. E.: Surg., Gynec. & Obst. **91**: 605, 1950.
25. Rosenthall, A. H., and Glass, M.: New York State J. Med. **51**: 2493, 1951.
26. Schattenburg, O. L.: West. J. Surg. **49**: 562, 1941.
27. MacFarlane, K. T., and Sparling, D. W.: Am. J. Obst. & Gynec. **51**: 343, 1946.
28. Sprague, J. R., and Sprague, E. A.: J. Internat. Coll. Surgeons **16**: 765, 1951.
29. Torpin, R.: Bull. Univ. Hosp. **5**: 1, 1944.
30. Ware, H. H., Jr.: West Virginia M. J. **44**: 49, 1948.
31. Ware, H. H., Jr., and Winn, W. C.: South. M. J. **39**: 44, 1946.
32. Word, B.: Surg., Gynec. & Obst. **92**: 333, 1951.
33. Zechel, G.: Arch. Surg. **41**: 646, 1950.
34. Priddle, H. D., Moulton, C. W., and Dennis, M. S.: Am. J. Obst. & Gynec. **64**: 1093, 1952.
35. Henderson, D. N., and Bean, J. L. M.: Am. J. Obst. & Gynec. **59**: 1225, 1950.
36. Whitacre, F. E., and Lynn, N. D.: Michigan State M. Soc. **47**: 285, 1948.
37. Campbell, R. M.: Am. J. Obst. & Gynec. **63**: 54, 1952.
38. Te Linde, Richard W.: Operative Gynecology, Philadelphia, 1946, J. B. Lippincott Company.
39. Dilworth, E. E., Mays, C. R., and Hornbuckle, L. A.: Am. J. Obst. & Gynec. **60**: 763, 1950.
40. Zarou, G. S., and Sy, A.: Am. J. Obst. & Gynec. **64**: 1338, 1952.
41. Novak, Emil: Gynecological and Obstetrical Pathology, ed. 2, Philadelphia, 1947, W. B. Saunders Company.
42. Stitt, E. R., Clough, Paul W., and Clough, Mildred C.: Practical Bacteriology, Haematalogy, and Animal Parasitology, ed. 9, Philadelphia, 1938, P. Blakiston's Son & Co.
43. Sunderman, F., William, and Boerner, Frederick: Normal Values in Clinical Medicine, Philadelphia, 1949, W. B. Saunders Company.

BOOSTER ESTROGEN THERAPY IN INFERTILITY*

WILLIAM C. WEIR, M.D., WILLIAM MCK. JEFFERIES, M.D., GERALD T. KENT, M.D., AND DAVID R. WEIR, M.D., CLEVELAND, OHIO

(From the Infertility Clinic of the Maternal Health Association of Cleveland and the Departments of Obstetrics and Gynecology and Medicine of the School of Medicine, Western Reserve University)

A SOUND rational basis for endocrine therapy in infertility problems is quite inadequate at the present time, because there is little accurate information regarding the hormone levels in the normal menstruating woman. The only available method of determining the quantitative and qualitative amounts of pituitary and ovarian hormones is biological assay, which supplies only an approximate indication of hormone levels. Nevertheless, the results of recent studies have been sufficiently consistent to suggest certain characteristic patterns of change in the normal menstrual cycle, and these in turn have suggested a new approach to the treatment of some cases of infertility in women.

D'Amour[1] found that in a normal cycle urinary estrogen excretion rose, reaching a peak on about the tenth day. This was followed by a drop and a secondary rise on about the twenty-first day. Immediately following the first estrogen peak, a short rise in the urinary gonadotropin excretion occurred. Farris,[2] using the rat ovary hyperemia method, also demonstrated a rise of gonadotropin excretion for four days in midcycle, and he thought that ovulation or the optimum day for conception was on the fourth day of this rise. Fevold, Hisaw, and Greep[3] found that, following the administration of estrogen in a rat, there was an increase of gonadotropin secretion. Brown and his associates[4] also have shown that gonadotropic hormone is released by the initial stimulating effect of estrogen.

These observations suggest that these changes may be related to ovulation. The rising estrogen probably reflects the development of the Graafian follicle. The peak or dropping of the estrogen may stimulate the pituitary which in turn produces a sudden rise in the gonadotropins. The elevated gonadotropin level may then effect final maturation of the ovum and rupture of the follicle. Following this the production of progesterone by the corpus luteum takes place.

The occurrence of ovulation has usually been demonstrated by indirect methods only. The production of progesterone by a functioning corpus luteum has been considered evidence of ovulation. The two methods commonly used to indicate the presence of this hormone are the biphasic basal body temperature curve and the presence of secretory endometrium on biopsy. In the light of present knowledge neither of these gives any clue as to the maturity or the quality of the ovum which may have been produced. Change in the exfoliated cells of the vagina and the cervix has also been used to determine the occurrence of ovulation. De Allende and Orias[5] have shown there is a rise in the percentage

*A grant from the Brush Foundation of Cleveland made this study possible.

of cornified epithelial cells in the vagina which reaches a peak on about the thirteenth or fourteenth day of the cycle or about the time of ovulation. This increase of cornified cells has been shown to be a direct result of the change in the amounts of estrogen present.

Fig. 1 shows graphically the relationship between the hormone levels, the normal basal body temperature curve, and the rise in the vaginal cell cornification counts. Ovulation is thought to occur on the fourteenth day under these conditions. The temperature rise in the last half of the cycle has been shown to be related to the production of progesterone by the corpus luteum and corresponds to the progesterone rise. The rise of epithelial-cell cornification has been shown to be due directly to estrogen.

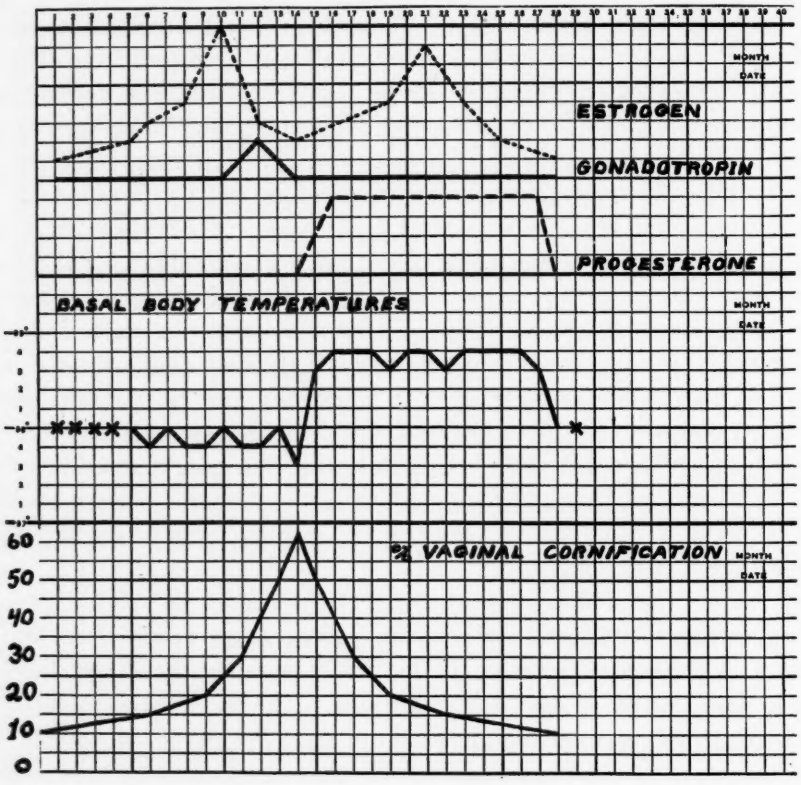


Fig. 1.—The time relationships in the normal cycle are shown between the levels of estrogen, gonadotropins, and progesterone, the basal body temperature curve, and the amount of cornified epithelial cells in the vaginal secretions. Under these conditions, ovulation or the optimum day for conception is thought to be the fourteenth day.

The four-day delay between the peak of estrogen excretion and the peak of cornification can probably be explained by the time element involved in the exfoliation of the cornified cells. The pattern of change following the administration of estrogen is consistent with this concept (Fig. 2). In this study a patient who had experienced long periods of amenorrhea and whose temperature charts revealed no evidence of ovulation was given Premarin, 1.25 mg. on three successive days and 2.5 mg. on the fourth day. Cornification counts, which had

been done every other day for twenty days to establish a base line, showed an immediate rise, reaching a peak four days after the largest and last dose of estrogen. This effect may be compared with Fig. 3, which shows the actual rise of cornified cells and the biphasic temperature curve in a normally menstruating patient. Hence it is evident that administration of a short course of estrogen in an increasing dosage can produce changes in cornification counts similar to those seen in the preovulatory phase of a normal cycle.

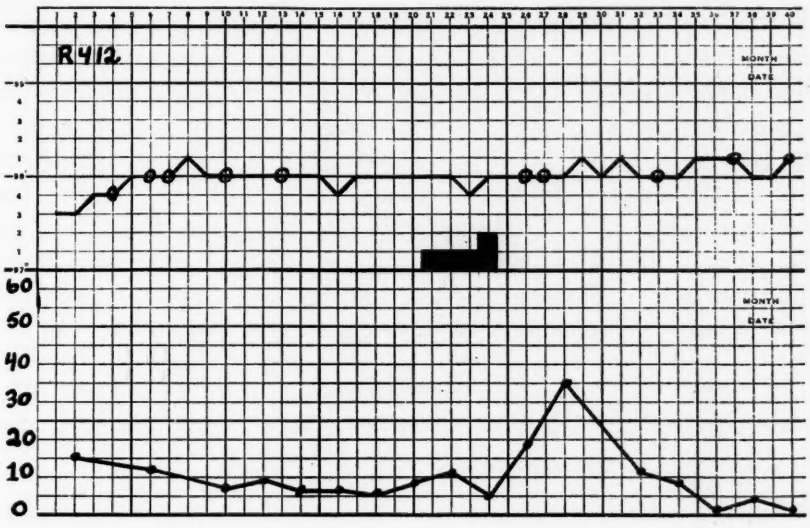


Fig. 2.—This shows the peak of cornification of the vaginal epithelial cells occurring four days after the maximum dose of the booster estrogen therapy given as follows: Premarin, 1.25 mg. on the twenty-first, twenty-second, and twenty-third days and 2.5 mg. on the twenty-fourth day of time of observation. On this and subsequent charts, circles indicate days on which intercourse occurred.

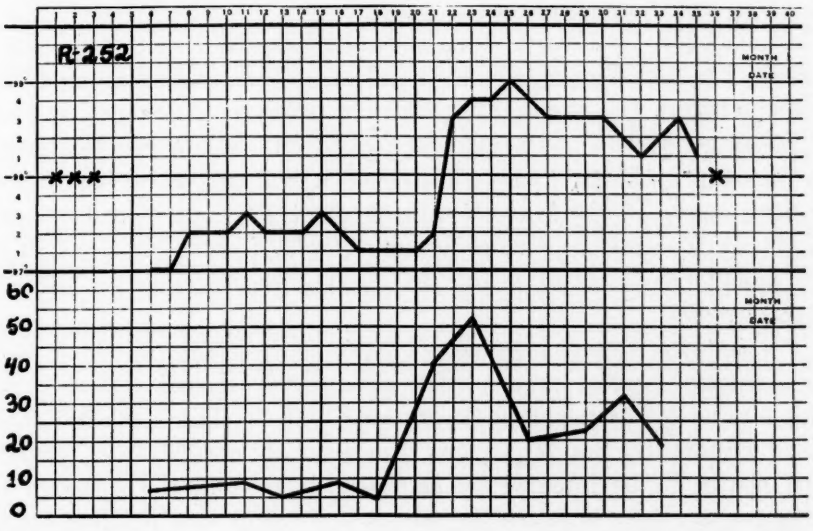


Fig. 3.—This shows the rise in amount of cornified cells in a normal cycle demonstrated by the temperature curve. The temperature curve is somewhat exaggerated and the peak of cornification occurs three days after apparent ovulation on the twentieth day.

Another factor in fertility which has been found to be related to hormonal output is the character of the cervical mucus. Normally prior to ovulation there is a typical clear mucus present, which accepts the penetrating sperm. Production and maintenance of this type of mucus is in part due to estrogen and it has been shown that when inadequate mucus is present it can be improved with estrogen.

The effect of estrogen upon the production of a proliferative endometrium is also well known.

On the basis of these considerations, it appears that an early peak of estrogen secretion in the menstrual cycle may be an important factor in the following developments: (1) stimulation of increased gonadotropin output by the pituitary, which is probably necessary for the normal maturation of the Graafian follicle and its rupture, releasing the ovum; (2) changing the character of the cervical mucus to a type which will more readily accept the penetrating sperm; and (3) preparation of the endometrium to receive the fertilized ovum. It, therefore, seemed reasonable to determine the effect of the administration of a rising dose of estrogen, or "booster estrogen," early in the menstrual cycle in certain cases of infertility.

Indications

The possibility of benefit from this type of therapy suggested its trial in the following four circumstances:

1. Irregular or Delayed Ovulation.—Many patients have cycles varying from four to ten or more weeks, but ending with a normal postovulatory temperature rise indicating a normal ovulation. Timing intercourse to achieve pregnancy in these cases is difficult as the number of fertile periods per year are reduced. By introducing an earlier peak of estrogen, it was hoped that ovulation could be induced to occur at a more normal time.

2. Inadequate or Short Temperature Rise.—The postovulatory rise of temperature has been shown to be the result of progesterone secretion. Although a slow temperature rise apparently does not preclude pregnancy in some cases, it may reflect a poorly functioning corpus luteum. Likewise a temperature rise of less than the usual 1° F. or a duration of the corpus-luteum phase of the temperature curve of less than the normal twelve to fourteen days may result from a poorly functioning corpus luteum. By increasing the peak of estrogen, a better gonadotropic response in turn might produce a better follicle, ovum, and corpus luteum.

3. Persistently Negative Simms-Huhner Test.—Some women are found to have inadequate cervical mucus with apparently normal temperature curves and with a persistently negative Huhner test four to six hours after intercourse, in spite of apparently normal semen. Since the character of the cervical mucus has been shown to be affected by estrogen, increasing the estrogen levels by booster estrogen might improve the mucus and result in a positive Huhner test.

4. No Abnormalities Noted.—Although all known criteria may indicate a normal ovulation, there is no way to be sure that a normal ovum is being pro-

duced or that the endometrium is properly prepared for implantation. Many couples without demonstrable defects but with long-standing infertility have been studied. Assuming that an abnormal ovum may be produced in some of these, increasing the estrogen peak may improve the gonadotropin response qualitatively and quantitatively and result in a more normal ovum. Similarly, an inadequately prepared endometrium not shown by the biphasic temperature curve might also be improved by such treatment.

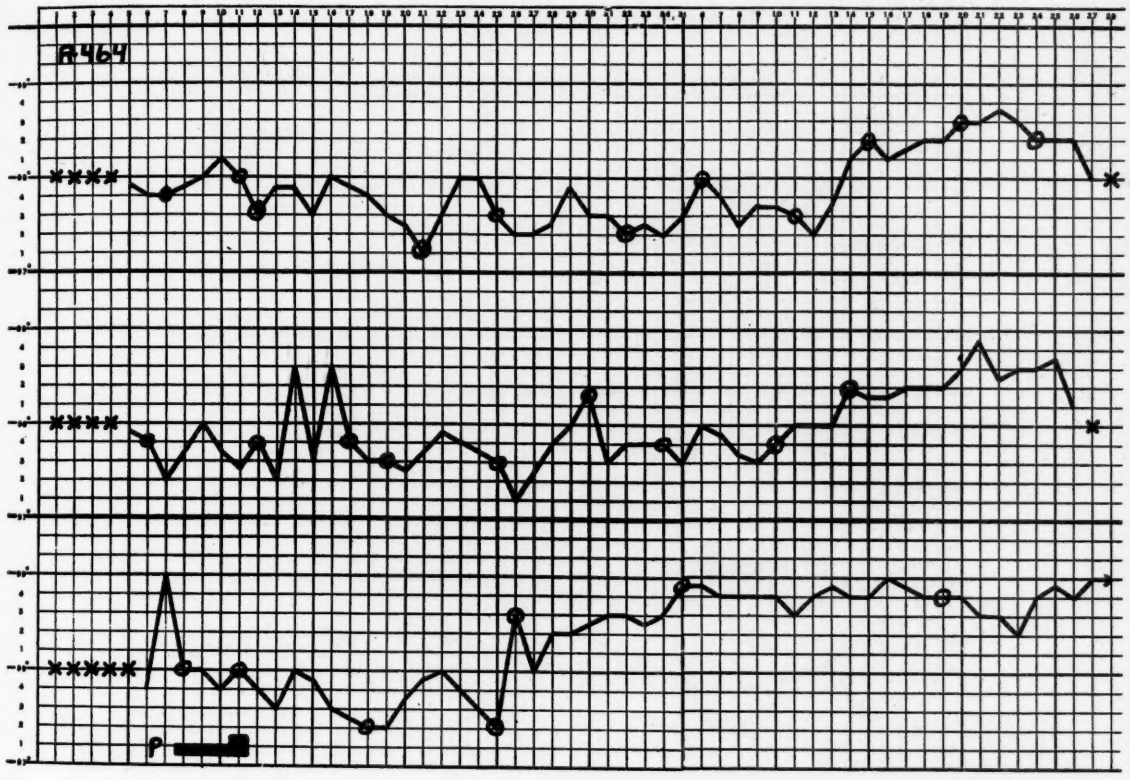


Fig. 4.—Effect on delayed ovulation. The first two cycles show ovulation on the forty-second and thirty-ninth days, respectively. Premarin, 1.25 mg., was given on the eighth, ninth, and tenth days and 2.5 mg. on the eleventh day of the third cycle. Ovulation appeared to be brought forward to the twenty-fifth day and conception occurred.

Certain difficulties in using this principle of therapy immediately presented themselves. Too much estrogen will suppress ovulation and the amount that will do this varies with the individual. It was found that a dosage and timing which seemed beneficial in one case would suppress or delay ovulation in another. The different estrogen substances used also apparently varied in their effectiveness in different individuals. As a result, effective amounts were arrived at by trial and error in each case. The time chosen to reproduce the peak probably is of considerable importance, particularly in those with irregular cycles. Another problem was the lack of enthusiasm on the part of some women for keeping temperature charts while attempts were made to reach an effective dosage. This may have been a factor in the lack of success in some cases.

Method

In the past five years in this clinic, booster estrogen therapy has been used in more than 100 of the first 400 couples studied, but only 85 of these had charts sufficiently complete to be included in this report. Four estrogenic substances were used and all were given orally:

1. Premarin, conjugated estrogens
2. Monozol, mono benzyl ether of stilbestrol
3. 17-Ethinyl estradiol
4. Diethylstilbestrol

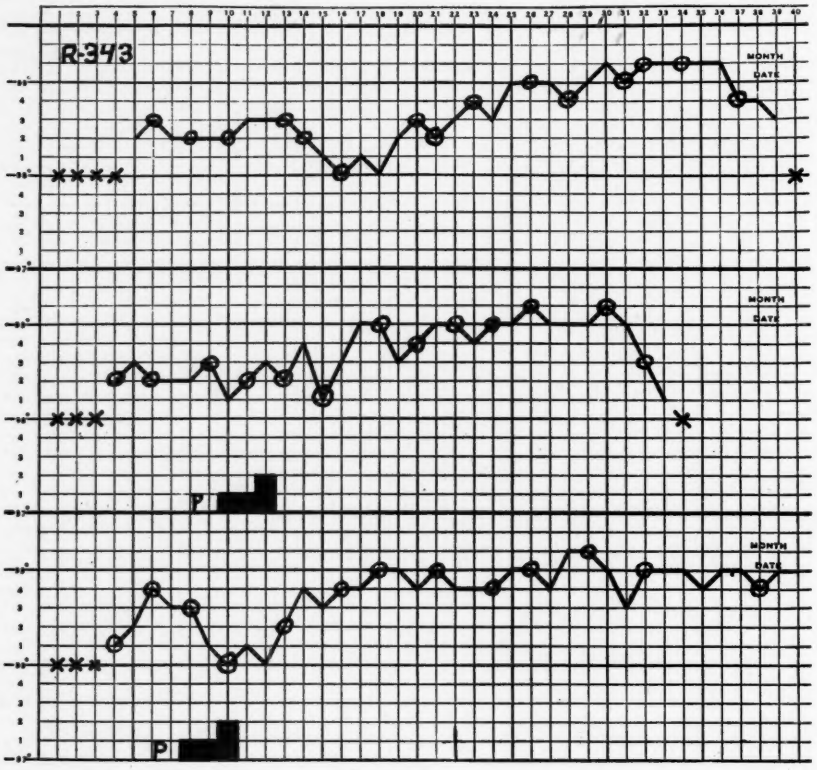


Fig. 5.—The effect on delayed ovulation and an improvement of the temperature curve. The first cycle shows ovulation on probably the eighteenth day with a rather sluggish rise. In the second cycle, Premarin, 2.5 mg. on the tenth and eleventh days and 5.0 mg. on the twelfth day, appeared to bring the ovulation forward to the fifteenth day and to improve the character of the rise. The same dosage given earlier in the third cycle and ending on the tenth day brought the day of ovulation forward to the twelfth day and conception occurred.

The schedule of therapy was such that a smaller amount was given on the first day of the course and a larger on the last, thus increasing the amount given. The minimum duration of therapy was two days and the maximum was five, the majority being three to four days. Table I shows the minimum and maximum dosages used on the first and last days of each course of therapy. The course of therapy was timed so that the last day with the largest dosage would fall on what was considered to be the most effective day of the cycle for the individual. This was usually on the tenth or the eleventh day of the cycle.

TABLE I. MAXIMUM AND MINIMUM DOSAGES OF ESTROGENIC SUBSTANCES

	MINIMUM FIRST DAY	MAXIMUM FIRST DAY	MINIMUM LAST DAY	MAXIMUM LAST DAY
Premarin R	1.25 mg.	2.5 mg.	2.5 mg.	5.0 mg.
Monozol R	1.5 mg.	3.0 mg.	3.0 mg.	6.0 mg.
17-Ethinyl estradiol	0.02 mg.	0.02 mg.	0.04 mg.	0.04 mg.
Diethylstilbestrol	0.1 mg.	0.2 mg.	0.2 mg.	0.4 mg.

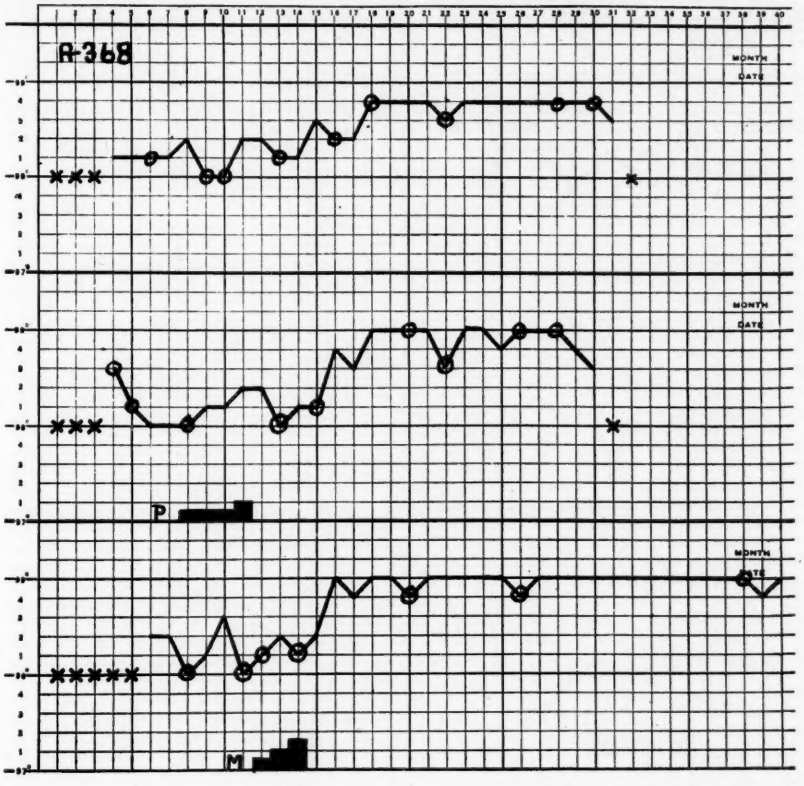


Fig. 6.—Improvement in the character of the temperature curve with two products. The first cycle at the top was characteristic of this patient's curves showing a small degree of elevation and a slow rise of the temperature curve. In the second cycle, Premarin, 1.25 mg., was given on the eighth, ninth, and tenth days of the cycle and 2.5 mg. on the eleventh, with a higher and sharper rise of the temperature. In the third cycle, Monozol, 1.5 mg., was given on the twelfth day of the cycle, 3.0 mg. on the thirteenth, and 4.5 mg. on the fourteenth, and again the character of the temperature rise was more normal and conception occurred.

Results

As stated previously, booster estrogen was given in four types of cases. The results were evaluated as follows:

1. Irregular or Delayed Ovulation.—When ovulation, as shown by a normal temperature curve, occurred earlier in the cycle following a course of booster estrogen than in previous cycles with no treatment, it was considered a positive response for that cycle. This is illustrated in Figs. 4 and 5.

2. Inadequate or Short Temperature Rise.—When the basal body temperature curve showed a sharper, higher, or more prolonged rise following a course of booster estrogen than in previous cycles, it was considered a positive response. This type of improvement is demonstrated in Figs. 6 and 7.

3. Persistently Negative Simms-Huhner Test.—When the Huhner test became positive following a course of booster estrogen in the same cycle in a case in which previous tests had been negative and with no other type of therapy to the cervix or to the husband, it was considered a positive response. This is shown in Fig. 7.

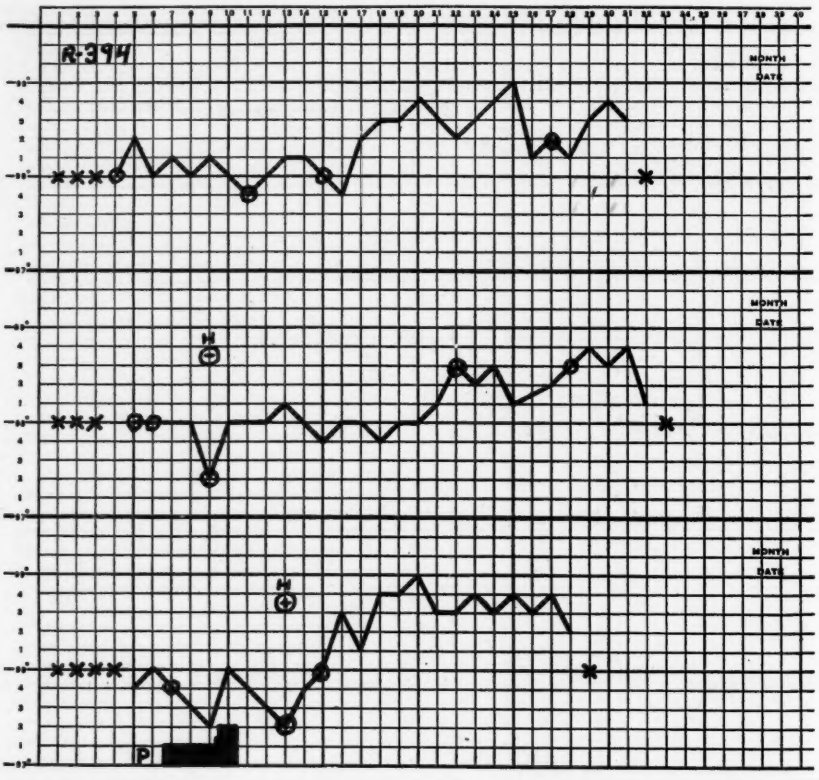


Fig. 7.—Improvement in the character of the temperature curve and change in the Huhner test. The first cycle is fairly normal but ovulation does not occur until the sixteenth day. The second cycle shows a poor ovulatory rise and the Huhner test was negative on the ninth day. In the third cycle, Premarin, 2.5 mg., was given on the seventh, eighth, and ninth days and 5.0 mg. on the tenth day. The character of the temperature curve was much improved and the Huhner test was strongly positive on the thirteenth day.

4. No Abnormalities Noted.—If pregnancy occurred in the cycle in which booster estrogen was given or in the following cycle without estrogen, and if no other specific therapy to the husband or wife had been used for the three previous cycles, it was considered a positive response. Fig. 8 is an illustration of this.

Included in this study are 85 women who received booster estrogen therapy for a total of 236 cycles in which temperatures were recorded. Forty of these women, or 47 per cent, had a positive response, as defined above, in one or more cycles, but not necessarily in all the cycles in which therapy was used.

Table II presents the number of cycles which showed positive and negative responses with the four different estrogenic substances used. Thirty-four per cent of the cycles showed apparent improvement with this type of therapy.

TABLE II. NUMBER OF CYCLES IN WHICH BOOSTER ESTROGEN THERAPY WAS USED

	POSITIVE RESPONSE	NEGATIVE RESPONSE	TOTAL
Premarin R	42	103	145
Monozol R	6	11	17
17-Ethinyl estradiol	9	23	32
Diethylstilbestrol	24	18	42
Total	81 (34%)	155 (66%)	236

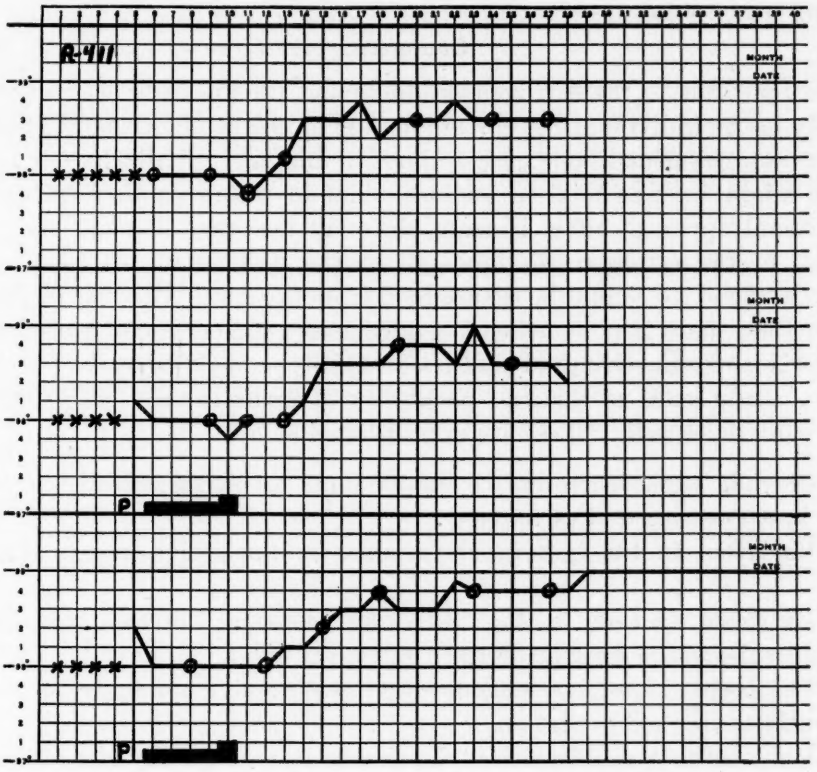


Fig. 8.—No apparent defects noted. The first cycle appears to be normal in all respects. Premarin, 1.25 mg., was given on the sixth, seventh, eighth, and ninth days and 2.5 mg. on the tenth day of the second cycle with no apparent change. Following an identical course of therapy in the third cycle, conception occurred.

TABLE III. NUMBER OF CASES IN WHICH BOOSTER ESTROGEN THERAPY WAS USED AND RESPONSES ACCORDING TO INDICATIONS AND SUBSTANCES ADMINISTERED

	TO REGULATE OVULATION		TO IMPROVE TEMP. RISE		TO IMPROVE CERVICAL SECRETION		NO ABNORMALITY		TOTAL	
	RESPONSE		RESPONSE		RESPONSE		RESPONSE		RESPONSE	
	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.
Premarin R	12	15	10	16	6	8	2	14	30	53
Monozol R	4	2	8	1	2	2	0	4	14	9
17-Ethinyl estradiol	2	2	2	4	0	0	0	2	4	8
Diethylstilbestrol	2	1	1	3	0	0	0	3	3	7
Total	20	20	21	24	8	10	2	23	51	77

Table III gives the number of cases which showed positive and negative responses to the therapy according to the indications for which the different estrogenic substances were given. A total of 51 positive responses were noted in the 40 patients who showed improvement. Since many of the patients were given more than one type of estrogen in different cycles and for more than one indication, the number of responses does not coincide with the number of individuals treated. This is demonstrated in Fig. 7 where the therapy in one patient was followed by improvement both in the temperature curve and in the cervical mucus.

Comment

The reactions to the estrogen products and the amounts used varied considerably in the individual. A certain dosage of one product would apparently result in improvement in one case and not in another. Similarly, one estrogen product might be beneficial in an individual in whom another estrogen had been without apparent effect in many different dosages. The optimal day for the peak of the estrogen administered or the best timing of the course of therapy in the cycle cannot be determined from the data. Because of these and other factors, there is no conclusive evidence as yet that one of these estrogen products is more effective than another for this type of therapy.

In a study such as this the possibility of error is very great and many factors contribute to it. These are in part listed below:

1. Possible slight variation in the amounts of physiologically active substances in the conjugated estrogens.
2. Variation in the individual response to the active agents that were used.
3. Extrinsic factors in the individual causing different responses in different cycles to the same amounts of estrogens given.
4. The lack of positive evidence that a normal basal body temperature curve indicates normal ovulation.
5. Many unknown defects contributing to infertility may alter the evaluation of the negative results.

Due to these uncontrolled factors, the data available to date cannot be tested by statistical analysis and until such a time as some kind of control can be established over most of these variables, evidence of statistical significance probably cannot be produced. However, in time, through more experience with dosages, and with a sufficiently large number of cases to study, it should be possible to evaluate this therapy in a more definite manner.

The rationale for this method of therapy seemed to justify a trial. During the time that it has been used a sufficient number of dramatic results have occurred so that it is felt that further study is justified. In the first 300 consecutively studied couples who were analyzed, 106 women conceived and a total of 125 pregnancies occurred. Although the therapeutic factor causing each of these pregnancies cannot positively be determined, it was felt that booster estrogen was probably responsible for seven of these, or 6 per cent.

Conclusions

1. A method of estrogen therapy has been presented which uses a rising dosage in the early part of the menstrual cycle in the hope of stimulating a release of increased amounts of gonadotropic hormone from the pituitary and thus increasing the possibility of producing a more normal ovulation at the normal time in the cycle.

2. The four situations in which this booster estrogen therapy has been employed are: (a) irregular cycles, (b) poor ovulatory responses as indicated by the biphasic temperature curve, (c) a persistently negative Simms-Huhner test, and (d) no apparent defects present.

3. Forty-seven per cent of the 85 women on whom this therapy was employed showed apparent improvement in one or more cycles.

4. Booster estrogen therapy was probably directly responsible for 6 per cent of the pregnancies which occurred in the first 300 couples studied in the clinic.

5. Results have been sufficiently favorable to indicate that the method warrants further study.

We are greatly indebted to the following:

James W. Reagan, M.D., and the Cytology Laboratory of the Institute of Pathology, Western Reserve Medical School, for the cornification cell counts.

S. H. Jaros, M.D., of Ayerst, McKenna & Harrison Limited, for supplying the Premarin used in this study.

Irwin C. Winter, M.D., of G. D. Searle & Company, for supplying the Monozol used in this study.

Mr. M. G. Albaugh, of E. R. Squibb & Sons, for supplying the diethylstilbestrol (Stilbetin) used in this study.

References

1. D'Amour, F. E.: Am. J. Obst. & Gynec. **40**: 958, 1940.
2. Farris, E. J.: Am. J. Obst. & Gynec. **50**: 14, 1946.
3. Fevold, H. L., Hisaw, F. L., and Greep, R. V.: Am. J. Physiol. **114**: 508, 1936.
4. Brown, W. E., Bradbury, J. T., and Jungck, E. C.: Am. J. Obst. & Gynec. **65**: 733, 1953.
5. De Allende, I. L. C., and Orias, O.: Cytology of the Human Vagina, New York, 1950, Paul B. Hoeber, Inc.

OVARIAN FUNCTION FOLLOWING INDUCED ABORTION*

MASAMICHI SUZUKI, M.D.,** AND TERUHIKO WATANABE, M.D.,

HIROSHIMA, JAPAN

(From the Laboratories of the Atomic Bomb Casualty Commission, Hiroshima, Japan)

ARTIFICIAL termination of early pregnancy has become one of the commonest gynecological procedures in Japan, since its legalization for socioeconomic reasons. Although studies of ovarian function following the termination of late pregnancy and spontaneous abortion have been published,[1-5] little attention seems to have been directed to this function after induced abortion. The present paper reports a study of the influence of abrupt mechanical termination of early pregnancy upon ovarian function.

Materials and Methods†

During the period from Oct. 18, 1949, to June 17, 1950, 47 patients who underwent induced abortion (mainly for socioeconomic reasons) consented to cooperate in a study of ovarian function following operation. One patient had two abortions during the period of study. The clinical diagnosis of uterine pregnancy was confirmed in 46 of these cases by histological examination of the uterine contents and/or by male frog pregnancy test.

The patients, all ambulatory, underwent operation on the day of admission to the hospital. Almost all the surgery was performed by the same gynecologist, under preoperative analgesia and local Novocain infiltration. The cervix was dilated, the uterine contents removed with a blunt curette, and the endometrium painted with tincture of iodine. The patients were instructed, while at the hospital, in taking and recording their basal temperatures sublingually, and noting subjective or objective symptoms. After several hours of rest, they were allowed to return home.

Approximately 2 to 3 weeks after operation, they returned to the hospital for biopsy. Endometrial tissue removed from the anterior and posterior walls of the uterine body near the fundus with Meigs'[6] biopsy curette was fixed in formalin or Bouin's fixative, brought through paraffin, and the sections stained with hematoxylin-eosin. Biopsy was repeated at 10 to 14 day intervals until the first supervening menstruation. In the subsequent cycles biopsies were performed whenever possible during the premenstrual phase.

Observations

Age, Parity, Duration, and Character of Gestation.—The 47 patients comprising this series were from 20 to 44 years of age, with an average of 29.8 years. Thirteen were past 35. All had been pregnant one or more times before the

*This work was sponsored by the Atomic Bomb Casualty Commission, National Academy of Sciences, National Research Council, with funds supplied by the United States Atomic Energy Commission.

**Gynecologist, Atomic Bomb Casualty Commission, since 1948.

†The clinical materials for this study were obtained from patients attending the Obstetrics-Gynecology Clinic at Hiroshima Prefectural Hospital by Teruhiko Watanabe, M.D., former assistant gynecologist, Atomic Bomb Casualty Commission, and now gynecologist-in-charge at Shita Hospital, Shizuoka Prefecture, Japan.

present gestation. The parity varied from gravida i, para 0, to gravida ix, para vii, with an average of 3.6 gestations and 2.8 children. Of the total 173 previous pregnancies, 8 (4.6 per cent) had terminated in spontaneous, and 27 (15.6 per cent) in induced abortion. In 19 patients the previous gestation also had been terminated artificially, and, in 15, the present conception had occurred within 6 months of the previous abortion.

In all but one instance the duration of gestation was calculated in days from the first day of menstruation of the last cycle to the day of operation. In one case in which conception occurred during postpartum amenorrhea without intervening menstruation the duration was estimated from the uterine size and the length of the uterine cavity at operation. The duration of gestation ranged from 35 to 121 days, and averaged 73.8 days.

The preoperative course of the subjects under study was considered normal; no histories suggestive of or indicating threatened abortion were obtained. Except for one case of typical hydatidiform mole discovered at operation, the pregnancies showed no gross abnormalities.

General Characteristics of Postabortal and Subsequent Menstrual Cycles.— Postoperative convalescence was uneventful in the majority of cases. In 43 of 48 induced abortions vaginal bleeding and spotting subsided within 10 days; however, in 4 cases it was necessary to repeat curettage on the fourth to seventeenth postoperative day because of excessive bleeding. A few patients complained of general malaise and an evanescent "cold." One developed moderate fever of three days' duration, diagnosed as pneumonia, on the twenty-second postoperative day.

In all but 2 patients, the first menstruation after induced abortion lasted 7 days or less. Specific inquiry into the comparative differences between present and previous menses of 20 patients revealed that 10 noted no change; 8 felt that menstruation was either prolonged or increased in amount; and 2 noted a scantier flow than usual. All subsequent menses were believed to be similar to menstruation before operation.

The duration of the postabortal cycle was considered to extend from the day of operation (day number one) to the day before the return of menstruation. Similarly other cycles were reckoned from the first day of menstruation to the day before the succeeding menstruation. The duration of menstrual cycles following induced abortion is shown in Table I. The shortest and the longest were 22 and 71 days, respectively. No significant difference in average duration was found between the preoperative, postabortal, and second to seventh subsequent cycles. The duration of pregnancy did not influence the length of either the postabortal or subsequent cycles. However, it was found that 28 of 48 postabortal cycles fell within the 25 to 34 day cycle, as compared with 23 of 30 preoperative cycles, 21 of 30 second cycles, and 29 of 33 subsequent cycles. A statistical analysis of this variability reveals a significantly wider variation in the duration of the menstrual cycle of the postabortal series. Furthermore, and surprisingly, the patients manifesting the normal secretory phase revealed this variation in cycle duration as frequently as those manifesting the anovular or atypical secretory phase.

TABLE I. DURATION OF MENSTRUAL CYCLE BY TYPE

DURATION IN DAYS	TYPE OF CYCLE							
	PREOPERATIVE		POSTABORTAL		II		II-VII	
	NUMBER	SUM	NUMBER	SUM	NUMBER	SUM	NUMBER	SUM
20-24	1	24	3	70	1	24		
25-29	13	367	14	375	8	222	18	499
30-34	10	314	14	449	13	412	11	345
35-39	4	150	8	295	5	184	2	70
40-44			2	87	2	85	2	81
45-49			4	183	1	49		
50 and over	2	113	3	192				
Total	30	968	48	1,651	30	976	33	995
Mean		32.3		34.4		32.5		30.2

Basal Body Temperature.—Forty-five patients of the series kept basal body temperature records for a total of 99 menstrual cycles. Forty-one records covered the postabortal cycle, and the remaining 58, Cycles II to VII (Table II). Besides the usual types of basal temperature curves—biphasic, monophasic, and bizarre—an unusually short biphasic curve was observed. Because of its association with abnormal histological endometrial patterns, the short biphasic type of basal temperature curve is distinguished from the usual normal biphasic curve, and is defined as a curve revealing a minimum of 0.4° F. shift, with persistent elevation in the latter part of the cycle, but the biphasic period is less than 9 days.

TABLE II. DISTRIBUTION OF TYPES OF BASAL TEMPERATURE CURVES IN MENSTRUAL CYCLES AFTER INDUCED ABORTION

TYPE OF BASAL TEMPERATURE CURVE	FREQUENCY MENSTRUAL CYCLE							TOTAL
	POST-ABORTAL	II	III	IV	V	VI	VII	
Biphasic	13	25*	14*	8*	4	1	1	66
Short biphasic	10	2	1	0	0	0	0	13
Monophasic	10	2	0	0	0	0	0	12
Bizarre	8	0	0	0	0	0	0	8
Total	41	29	15	8	4	1	1	99

*Includes records with persistent thermal elevation due to pregnancy.

The duration of the biphasic components of the basal temperature curve was reckoned as follows:

1. Low, or proliferative period, from day one of menses to the beginning of the shift.
2. Thermal shift, from the end of the sustained low period to the beginning of the persistent high period.
3. Persistent high period, from the beginning of the sustained high to the day before the succeeding menstruation.

Sixty-six biphasic-type basal temperature curves, including 4 with persistent elevation which proved subsequently to be due to pregnancy, were recorded. In the postabortal cycle, only 13 of 33 basal temperature curves (bizarre type excluded) were of this type. Rapid progressive increase in incidence of the biphasic type is shown by its occurrence in 25 of 29 second, and in all subsequent, cycles, respectively.

The duration of the thermal shift was found to average 2.8 days, the longest being 8 days (stepladder). The average high persistent period was 10 days, with a range of 4 through 14 days. The mean of the biphasic period (thermal shift plus the high persistent period) was 12.8 days. Forty-six of 62 biphasic curves (4 biphasic curves with persistent thermal shift were excluded) fell into the 12 to 15 day periods. No significant difference in the pattern of the biphasic components of the postabortal and subsequent cycles was noted.

Thirteen short biphasic curves were recorded by 12 patients, during the first 3 cycles after abortion. Ten, representing 30 per cent (bizarre type excluded), were found in the postabortal cycle; 2 patients who had monophasic curves in the postabortal cycle had short biphasic curves in the second cycle, with a repetition in the third cycle in one patient. The thermal shift in this type of curve varied from 1 to 5 days, and the high persistent period from 2 to 7 days. The average length of the short biphasic period (thermal shift plus high persistent period) was 5.5 days, the shortest being 3 days. Corresponding endometrial biopsies taken within 11 days of the succeeding menstruation will be discussed later in this paper.

Twelve monophasic curves were recorded by 10 patients within the first two cycles after abortion: This type of curve appeared in 10 of 33 postabortal cycles and in 2 of 29 second cycles. Two patients had monophasic curves in successive cycles; one had a short biphasic curve; and the remaining 7 had normal biphasic curves in the second cycle. In most cases, the slightly elevated temperature following the operation dropped either gradually or abruptly to the usual lower level. In 4 the monophasic curve prevailed at or near the same level as that immediately following operation, with a definite drop of 0.4 to 0.6° F. at menstrual onset. It was thought possible that the biphasic type of curve might have remained obscured in these cases; however, the discovery of a proliferative endometrium within 2 to 7 days of the menstrual onset definitely rules against this.

Eight bizarre types of basal temperature curves were seen only in the postabortal cycle. Five can be attributed to extrinsic factors. For 3 no definite cause could be discovered, and as no further records were kept by 2 of these latter patients, the persistence is not known. The third patient's subsequent record revealed a biphasic curve with persistent elevation, due to pregnancy.

Endometrium.—Analysis fails to reveal a significant difference between the lengths of the menstrual cycles of biopsied as against unbiopsied cases. Further, the phase at which the biopsy was taken apparently did not alter the duration of the cycle significantly; or did repeated biopsies.

The progressive development of the endometrial histological pattern during the secretory phase of the normal menstrual cycle is sufficiently uniform to permit dating the endometrium with fair accuracy during this phase.[7, 8] Accordingly, the histological pattern of the endometrium obtained within 11 days of the next menstruation was classified into three categories: Normal secretory (NSP), atypical secretory (AtSP), and absent secretory phase (AbSP) (Table IV). The normal secretory phase includes those endometria revealing secretory changes falling within 3 days of the true endometrial dating; the atypical

secretory phase, those revealing secretory changes with development delayed beyond 3 days of the true dating. The absent secretory phase corresponds to a proliferative endometrial pattern and is self-defined.

One hundred twenty-one endometrial biopsies were performed upon 47 patients over 6 consecutive menstrual cycles after induced abortion. Of these, 67 were performed within 11 days of the supervening menstruation: 33 biopsies in 32 patients during the postabortal cycle and 34 during 32 subsequent cycles (II to VII).

The distribution of histological endometrial patterns after induced abortion is shown in Table III.

TABLE III. DISTRIBUTION OF HISTOLOGICAL ENDOMETRIAL PATTERN FREQUENCY IN THE MENSTRUAL CYCLES FOLLOWING INDUCED ABORTION

HISTOLOGICAL PATTERN	FREQUENCY MENSTRUAL CYCLE							TOTAL
	POST-ABORTAL	II	III	IV	V	VI	VII	
Normal secretory	13	19	5	1	3	1	0	42
Atypical secretory	10	2	0	0	0	0	0	12
Absent secretory	9	1	0	0	0	0	0	10
Total	32	22	5	1	3	1	0	64

As in the basal temperature study, where only 39 per cent of the curves were of the biphasic type, the relatively low incidence (13 of 32 endometria) of the normal secretory pattern in the postabortal cycle is significant; rapid increase in its frequency in subsequent cycles—19 of 22 in Cycle II and all in Cycles III to VII—indicates the rapid return of ovarian function to normalcy after induced abortion.

The basal body temperature and endometrial biopsy methods have been discussed separately to permit evaluation of each procedure. The basal temperature in this investigation was used only as an adjunct to the endometrial biopsy, since the latter is generally accepted to be the most reliable indirect clinical method for the routine investigation of ovarian function in human beings. But endometrial biopsy at the proper time is not always possible, and the basal temperature method is useful to achieve continuity of the study by retaining those patients on whom biopsies could not be performed within the 11 day premenstrual period. The basal temperature was clinically useful because, except in rare instances, it indicates the presence or absence of ovulation, provided the fallibility of the patient is taken into consideration. Also, evidence is strong that the temperature rise and maintenance may be attributed to progesterone or the progesterone-estrogen combination in systemic circulation.[9]

In 48 cycles, both basal temperature records (excluding the bizarre types) and endometrial specimens were available for study. There was no discrepancy between the histological patterns of the endometrium and the type of basal temperature curve in 41 cycles—29 with the normal secretory-normal biphasic, 5 with the atypical secretory-short biphasic, and 7 with the absent secretory-monophasic pattern.

Discrepancies between the findings with the two methods were noted in 7 cycles involving 6 patients. In these the determination of ovarian function was based upon the histologic pattern of the endometrium rather than on the basal temperature record.

Ovarian Function Following Induced Abortion.—Table IV shows the detailed distribution of types of endometrial and basal temperature findings classified according to the duration of gestation and menstrual cycles. A summary of these two methods in terms of normal and abnormal ovarian function is shown in Table V. During the postabortal cycle 26 of the 42 cases, or 62 per cent, reveal an abnormal function in which the atypical secretory and anovular pictures are distributed equally. Return to normality in ovarian function occurs rapidly; 29 of 33 second cycles and all subsequent cycles revealed normal progestational changes.

TABLE IV. DISTRIBUTION OF ENDOMETRIAL AND BASAL TEMPERATURE PATTERNS ACCORDING TO DURATION OF GESTATION AND MENSTRUAL CYCLES

METHOD	PATTERN	DURATION OF PREGNANCY IN DAYS					TOTAL
		35-55	56-76	77-97	98-118	119-129	
Postabortal Cycle.—							
Endometrium with or without basal temperature	NSP	7	6	0	0	0	13
	AtSP	1	2	5	1	1	10
	AbSP	1	3	4	1	0	9
Only basal temperature	Biphasic	2	0	0	1	0	3
	Short biphasic	2	0	0	1	0	3
	Monophasic	0	2	2	0	0	4
Cycle II.—							
Endometrium with or without basal temperature	NSP	7	7	3	1	1	19
	AtSP	0	2	0	0	0	2
	AbSP	0	0	1	0	0	1
Only basal temperature	Biphasic	2	3	4	1	0	10
	Short biphasic	0	0	0	0	0	0
	Monophasic	0	0	1	0	0	1
Cycles III to VII.—							
Endometrium with or without basal temperature	NSP	3	4	2	1	0	10
	AtSP	0	0	0	0	0	0
	AbSP	0	0	0	0	0	0
Only basal temperature	Biphasic	5	13	3	1	0	22
	Short biphasic	0	0	0	0	0	0
	Monophasic	0	0	0	0	0	0

TABLE V. OVARIAN FUNCTION IN POSTABORTAL AND SUBSEQUENT CYCLES

OVARIAN FUNCTION	DURATION OF PREGNANCY IN DAYS					TOTAL	
	35-55	56-76	77-97	98-118	119-126		
Postabortal Cycle.—							
Normal	9	6	0	1	0	16	
Abnormal							
Atypical	3	2	5	2	1	13	26
Anovular	1	5	6	1	0	13	
Cycle II.—							
Normal	9	10	7	2	1	29	
Abnormal:							
Atypical	0	2	0	0	0	2	4
Anovular	0	0	2	0	0	2	
Cycles III to VII.—							
Normal	8	17	5	2	0	32	
Abnormal:							
Atypical	0	0	0	0	0	0	0
Anovular	0	0	0	0	0	0	

In the postabortal cycle this significantly increased abnormal ovarian function is statistically shown to be related to the duration of pregnancy. The average duration of gestation of patients with normal secretory pattern was 57.9 days, and of those with an atypical or absent secretory pattern, 78.3 and 76.3 days, respectively. When the patients with abnormal ovarian function are distributed according to duration of pregnancy, 4 of 13 fall into the 35 to 55 day gestational group, 7 of 13 in the 56 to 76 day group, and 15 of 16 beyond 76 gestational days.

No significant difference was found between the lengths of the postabortal cycle of those with normal and those with abnormal ovarian function.

In 36 patients whose subsequent menstrual cycles were studied, 7 became pregnant, 4 during the second cycle and the others during the third, fourth, and sixth cycles. Ovulation was demonstrated in 16 patients in the postabortal cycle; conception during this cycle is therefore possible. Abstinence or infrequent coitus immediately after operation was probably the cause of the infrequency of conception during the postabortal cycle.

Some degree of lactation was still present from previous term pregnancies in 12 patients. Three had one or more induced abortions between the present and previous term pregnancies. This prolonged lactation apparently exerted no significant influence upon ovarian function after induced abortion.

Comment

A high incidence of anovulatory and atypical secretory patterns has been found to occur in the postabortal cycle, especially in subjects with gestation beyond 76 days. The reason for greater frequency of abnormal ovarian function in this group than in the early stages of pregnancy is not known.

In the normal menstrual cycle the interplay of follicle-stimulating and luteinizing hormones of the anterior pituitary gland upon the ovarian follicles results in the production of estrogen, which in turn stimulates proliferation of the endometrium. The exact mechanism of ovulation is still not clear; however, after sufficient growth of the follicles, luteinizing hormone, in the presence of a trace of follicle-stimulating hormone, leads to ovulation with maintenance of a newly formed corpus luteum for about two weeks. Progesterone released from the active corpus luteum converts the proliferative phase of the endometrium to the secretory phase, which persists for about two weeks; then withdrawal of estrogen and progesterone results in menstruation.

The inability of the normal mechanism to function following induced abortion may be related to the abrupt termination of pregnancy, with the resultant sudden withdrawal of placental hormones, especially chorionic gonadotropin. The subsequent degeneration of the corpus luteum of pregnancy was not a factor in the change of endometrial pattern, as the corpus luteum is probably not a secretory organ after 60 or 90 days of gestation. These abrupt hormonal changes may induce ovarian unresponsiveness to the normal secretion of anterior pituitary hormones or unresponsiveness of the anterior pituitary gland itself with failure to release its hormones normally, and consequent anovulation or abnormal ovulation.

Although the average length of the menstrual cycle in the postabortal series did not differ significantly from the preoperative or Cycles II to VII series, the degree of variation in the duration of the menstrual cycle within the postabortal series was significantly greater than in the preoperative or Cycles II to VII series. This wide variation was observed as frequently among the patients who manifested normal ovarian function. Thus, the factor or factors controlling the rhythmic recurrence of menstruation were affected during the first menstrual cycle after induced abortion. This was true whether because of cyclic withdrawal of estrogen in an anovulatory cycle or of estrogen-progesterone in normal or atypical secretory cycles.

Studies of ovarian function after spontaneous abortion have been reported by Rutherford and Mezer,[2] Stewart,[3] and recently by Sharman.[5] Stewart and Rutherford and Mezer have pointed out that ovulation is almost immediately re-established in the first cycle after spontaneous abortion. Sharman in 1951 studied 42 patients ranging from 19 to 47 years of age. The duration of the pregnancy was less than 126 days in 40 of these patients. The premenstrual endometrium was studied in 33 cases during the postabortal cycle; 10 exhibited an anovular pattern. No evidence of the absence of ovulation was observed in subsequent cycles; furthermore, once the normal secretory pattern was established, all subsequent cycles were secretory.

This study reveals the incidence of an anovular pattern in the postabortal cycle identical to that reported by Sharman; however, an additional finding of an atypical secretory pattern in approximately one-third of our postabortal cases appears to indicate a greater disruption of ovarian function after induced than after spontaneous abortion. We are well aware of the hazard of comparing our data with those of Sharman without a knowledge of the uniformity of the samples. Nevertheless, it is reasonable to assume that reduction in hormone production by placental tissue occurs gradually, since varying degrees of placental degeneration are found in many cases of spontaneous abortion.

Further clinical and endocrinologic investigations of the cause or causes of abnormal ovarian function after abortion are needed. One study under consideration will attempt to correlate the endometrial and basal temperature patterns with direct observation of the ovaries in patients who undergo tubal ligation for sterilization 3 to 4 weeks after induced abortion.

Summary

1. The ovarian function of 47 patients following a total of 48 induced abortions performed mainly for socioeconomic reasons was studied by endometrial biopsy and basal temperature methods.

2. One hundred twenty-one endometrial biopsies were performed and 99 basal temperature records were obtained during the investigation. Sixty-seven biopsies were performed within 11 days of the menstrual onset.

3. The ovarian function in 43 cases was studied during the postabortal cycle.

A. Twenty-six patients showed abnormal ovarian function. An anovular picture was present in half of these.

B. A high incidence of abnormal function was found to be significantly related to the duration of pregnancy. While only 4 of 13 patients with gestations from 35 to 55 days showed abnormal patterns, the proportion rose to 7 of 13 in the 56 to 76 day group, and to 15 of 16 who were beyond the seventy-sixth day of gestation.

C. Although no significant difference was found in the average length of the postabortal cycle as compared with the preoperative and second to seventh cycles, the degree of variation in the length of the menstrual cycles within the postabortal series was significantly greater than within the other series, indicating that the factor or factors controlling the cyclic rhythmicity of menstruation are affected in the postabortal cycle by the abrupt termination of the pregnancy.

4. Thirty-six patients were followed after the postabortal cycle for a total of 65 menstrual cycles (second to seventh cycles). Return to normalcy of ovarian function after the postabortal cycle occurred rapidly since 29 of 33 second cycles and all subsequent cycles revealed progestational changes.

5. The mechanism of abnormal ovarian function in the postabortal cycle is not known, but may be the result of either ovarian or anterior pituitary gland insensitivity induced by abrupt and drastic removal of the placenta and the consequent withdrawal of all of its hormones.

We wish to acknowledge the cooperation given us by Dr. Y. Wakimoto, Hiroshima Prefectural Hospital; also to thank Mr. Newton Morton of the ABCC for his statistical help, and Dr. Grant Taylor, director of ABCC, and Dr. E. T. Engle, College of Physicians and Surgeons, Columbia University, for their encouragement.

References

1. Lass, P. M., Smelser, J., and Kurzrok, R.: Endocrinology 23: 39, 1938.
2. Rutherford, R. N., and Mezer, J.: J. A. M. A. 119: 124, 1948.
3. Stewart, H. L.: Am. J. Obst. & Gynec. 59: 563, 1950.
4. Udesky, I. C.: Am. J. Obst. & Gynec. 59: 843, 1950.
5. Sharman, A.: Fertil. & Steril. 2: 371, 1951.
6. Meigs, J. V.: Am. J. Obst. & Gynec. 38: 161, 1931.
7. Hertig, A. T.: In National Committee on Material Health, Inc., Earl T. Engle, editor: Proc., Conference on Diagnosis of Sterility, Springfield, Ill., 1946, Charles C Thomas.
8. Moyes, R. W., Hertig, A. T., and Rock, J.: Fertil. & Steril. 1: 3, 1950.
9. Buxton, C. L.: Fertil. & Steril. 2: 299, 1951.

EXTRAPULMONARY TUBERCULOSIS AND PREGNANCY

GEORGE SCHAEFER, M.D., R. GORDON DOUGLAS, M.D., AND
IRVING H. DREISHPOON, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology of the Cornell University Medical College and The Woman's Clinic of the New York Hospital)

EXCEPT for a few case reports, little has appeared in the literature on the management of the pregnant patient with extrapulmonary tuberculosis. It has been estimated that 10 to 20 per cent of patients with pulmonary tuberculosis manifest extrapulmonary lesions.[1] Since the incidence of pulmonary tuberculosis complicating pregnancy is between 1.5 and 2 per cent in those clinics employing routine photoroentgens in all antepartum patients,[2, 3] one might expect to find extrapulmonary tuberculosis in approximately 0.15 to 0.4 per cent of pregnant patients. In 67,232 pregnancies (61,732 full-term and premature deliveries and 5,500 abortions) at the New York Lying-In Hospital from September, 1932, through December, 1951, there were 71 cases of extrapulmonary tuberculosis (0.1 per cent).

Statistics

There were 54 patients in our series, 45 of whom had 59 full-term and premature deliveries, 6 who had 8 therapeutic abortions, and 4 who had spontaneous abortions. One patient had a premature delivery and 2 years later had a therapeutic abortion. Forty-nine of the patients were white and 5 were Negro. The age incidence is shown in Table I.

TABLE I. AGE OF PATIENTS WITH ENTRAPULMONARY TUBERCULOSIS

YEARS	NUMBER
15-19	2
20-24	7
25-29	24
30-34	25
35-39	11
40-45	2
	71

TABLE II. SYSTEMS INVOLVED IN EXTRAPULMONARY TUBERCULOSIS AND PREGNANCY

	NO. PATIENTS	NO. DELIVERIES	NO. ABORTIONS
Osseous	21	22	6
Renal	18	20	2
Lymph node	9	9	2
Intestinal	3	6	0
Pericardial	1	1	1
Miliary	1	1	0
Peritoneal	1	0	1
	54	59	12

Three per cent of our patients were under 20 years of age and 3 per cent were over 40 years. Ninety-four per cent were between 20 and 40 years.

We have listed the various extra-pulmonary systems involved in Table II. The osseous and renal systems were most frequently involved and accounted for 72 per cent of the cases. Tuberculosis of the lymph nodes occurred in 17 per cent and the four other systems involved comprised 11 per cent of the patients. It is significant to record no known single instance of tuberculosis in any part of the genital tract.

Only the full-term and premature deliveries will be analyzed in this paper. The therapeutic abortions performed for extrapulmonary tuberculosis will be reviewed in another report together with therapeutic abortions performed for pulmonary tuberculosis.

Pathogenesis of Extrapulmonary Tuberculosis

The pathogenesis of tuberculosis has been described by Ornstein and Ulnar.[1] "Immediately following the primary inoculation with tubercle bacilli there is a free circulation of organisms throughout the body. This is the time when isolated nonpulmonary foci are established. If the bacilli become fixed in an organ they may proliferate at a later date." The original site of inoculation may heal and disappear and only the extrapulmonary focus remain. This state of affairs continues for ten to fourteen days until the allergic state is established. Once this change has taken place the free wandering of bacilli ceases, and they become fixed in whatever site they may happen to be situated when allergy occurs. Thereafter, so long as allergy remains, the organisms do not migrate through the blood stream as they did before sensitivity was established. If the blood should revert to a stage of anergy, however, circulation of organisms recurs as was noted in the initial phase of infection.

Osseous Tuberculosis

Twenty-two deliveries occurred in 17 patients with osseous tuberculosis. Two patients had 3 pregnancies and 1 had 2 pregnancies. In 15 patients there was no evidence of pulmonary tuberculosis and in 2 patients an inactive pulmonary lesion was present. The spines and the hip bones were each involved 10 times, the ankle once, and the ribs once. Pregnancy occurred from 4 to 33 years after the onset of tuberculosis; the average was 17 years.

Obstetrical Course.—The type of delivery in these patients was as follows: 13 had normal spontaneous deliveries, 4 had low forceps, 2 had midforceps, and 3 had cesarean sections. Only 1 of the sections was done for tuberculosis in a patient who had a previous hip fusion. The other 2 sections were done for obstetrical indications, one for premature separation of the placenta and the other for placenta previa.

All of the 17 patients with osseous tuberculosis showed no change in their condition following delivery.

Comment.—Wilkinson,[4] on the basis of an analysis of 27 case histories, states that there appear to be good grounds for reassuring the married woman

who has suffered from skeletal tuberculosis regarding the prospect of a normal pregnancy. Gibson[5] reports 3 patients with Pott's disease who were entirely unaffected by pregnancy.

Recent reports on the use of streptomycin in skeletal tuberculosis have been encouraging. Bickel and co-workers[6] report the use of streptomycin in 16 nonpregnant patients with tuberculosis of bones and joints. Response to streptomycin was considered favorable in 9 cases, fair in 1, of no benefit in 4, and too recent to evaluate in 2. They recommend 1 Gm. of streptomycin daily for 90 days as a satisfactory course of treatment. Bosworth[7] used streptomycin in 95 nonpregnant patients who had bone or joint tuberculosis with mixed infections and sinuses. He concluded that streptomycin represents a tremendous advance in the treatment of skeletal tuberculosis but was skeptical as to the ability of streptomycin alone to heal a bone or joint lesion permanently.

Bosworth[8] also reported on the use of one of the isonicotinic hydrazides (iproniazid) in 34 patients with various extrapulmonary foci. Among the patients treated, there were 30 lesions of bones and 22 of joints. The response was excellent, particularly as to relief of pain. Further investigation with this drug is being continued.

The results in the 22 deliveries in our 17 patients were good and the consensus of opinion in the literature is that osseous tuberculosis is not a contraindication to pregnancy. The antituberculosis drugs that have been useful in the nonpregnant patient with skeletal tuberculosis may be used when this condition complicates pregnancy.

Renal Tuberculosis

Sixteen patients with renal tuberculosis had 20 deliveries; four patients were pregnant on 2 occasions. Twelve patients had inactive pulmonary tuberculosis which had been arrested for many years and in 4 patients no pulmonary lesion was demonstrable.

The right kidney was involved in 9 patients, the left in 6, and the disease was bilateral in 1 patient. In 9 patients nephrectomy was performed before the onset of pregnancy. The shortest period between nephrectomy and conception was 2½ years, the longest 9 years, and the average time 5 years. In 2 patients nephrectomy was performed during the seventh month of gestation and in 2 patients it was done 3 weeks post partum. Three patients did not have nephrectomy.

Obstetrical Course.—Of the 20 pregnancies, 11 terminated in normal spontaneous deliveries, 3 in low forceps deliveries, 2 in breech deliveries, and 4 in cesarean section. Renal tuberculosis was the indication for section in 3 patients and a prolonged, 57 hour desultory labor was the indication in the fourth.

Morphine sulfate was used in 13 instances and meperidine in 7 for analgesia. For the vaginal deliveries, ether was used 4 times, nitrous oxide 5 times, local anesthesia 6 times, and no anesthesia once. For the cesarean sections, local anesthesia was used 3 times and ether once.

Eighteen of the 20 infants were born living and in good condition. One premature infant that weighed 1,690 grams died 7 hours after cesarean section and 1 infant was deadborn and macerated.

Comment.—Renal tuberculosis is a rare complication of pregnancy. In our series it occurred once in every 3,086 deliveries. Cibert, Gayet, and Mafart[9] found 23 associated pregnancies in 887 patients with renal tuberculosis. They believe that when renal tuberculosis is diagnosed before the last trimester the patient should be allowed to deliver before nephrectomy is done. Pugh,[10] Curtis,[11] and Stevens[12] do not consider pregnancy a contraindication to nephrectomy in unilateral renal tuberculosis and advise early operation to prevent the spread of the tuberculous disease. Lissack[13] reports upon a patient whom he delivered 4 times subsequent to nephrectomy for tuberculosis. Falls[14] has watched 5 patients who had one kidney removed for tuberculosis, and who subsequently became pregnant, go through pregnancy with no ill effect on the mother except that 2 of the 5 developed evidence of pre-eclampsia.

Case reports on the use of streptomycin for renal tuberculosis in pregnancy have been published by Faugere,[15] Kistner,[16] and Watson.[17] They found improvement in the patient's condition, although adequate follow-up in their cases is not yet available to determine whether these patients will become free of disease. Streptomycin has also been used in bilateral renal tuberculosis occurring during pregnancy by Nesbit[18] with arrest of the tuberculosis during gestation. It is the opinion of Pfeutze, Hinshaw, and Feldman[19] that streptomycin possesses palliative value in many cases of genitourinary tuberculosis and may bring the disease to temporary arrest in a small percentage. However, at this time, streptomycin is not considered a substitute for the surgical treatment of renal tuberculosis. The chemotherapy of genitourinary tuberculosis with isonicotinic acid hydrazide (Rimifon) has been studied by Greenberger[20] who noted an improvement in the general condition of the patients but no bacteriologic "cure."

It appears to be the most prevalent opinion that unilateral renal tuberculosis complicating pregnancy should be treated as in the nonpregnant patient, namely by pre- and postoperative use of streptomycin and para-aminosalicylic acid and by nephrectomy as soon as indicated by the patient's condition.

Lymph Node Tuberculosis

Nine deliveries occurred in 7 patients with tuberculosis of the lymph nodes; one woman had 3 deliveries. The cervical nodes were involved in all 7 patients. In 5 instances there was no evidence of pulmonary tuberculosis and in 2 patients there was evidence of a minimal active pulmonary lesion. On 3 occasions excision of the tuberculous gland was performed during gestation and in 4 patients the diagnosis of lymph node tuberculosis was made from 3 to 10 years before conception.

Obstetrical Course.—Five of the 9 deliveries were spontaneous, 2 were by low forceps, and 2 by midforceps. Morphine sulfate was used for analgesia 4

times, meperidine twice, pentobarbital sodium once, and no analgesia once. The anesthesia was gas, oxygen, ether in all cases. Nine normal infants were born.

Comment.—The predilection for the cervical nodes in hematogenous infection is probably a result of their lowered resistance due to previous infections of a different nature. The human type of tubercle bacillus, rather than the bovine, is responsible for most cases of lymph node disease in spite of a widespread impression to the contrary. Lester[21] advises excision of lymph node tuberculosis with eradication of tuberculosis elsewhere in the body and has found streptomycin and para-aminosalicylic acid valuable additions to the therapy of tuberculous lymphadenitis. It would appear that this form of therapy is also applicable to the pregnant patient.

Intestinal Tuberculosis

Six full-term deliveries occurred in 3 patients with intestinal tuberculosis, each patient delivering twice. All three had minimal inactive pulmonary tuberculosis for 2 to 10 years before conception. One patient had tuberculous fistulas about the perineal and anal regions. The portions of the intestinal tract involved were cecum, colon, and ileum.

Obstetrical Course.—There were three normal spontaneous deliveries, one low forceps delivery, and 2 cesarean sections in this group. The 2 sections were done on the patient who had extensive perineal and anal tuberculous fistulas. This patient also received streptomycin and para-aminosalicylic acid for one month after delivery of her second child with marked improvement in her condition. Analgesia was morphine in 4 cases and meperidine in 2 instances. Delivery was under local anesthesia in 5 patients (the two sections were performed under local anesthesia) and ether in one patient. Five normal infants were born and one infant with erythroblastosis was deadborn.

Comment.—The incidence of intestinal tuberculosis varies from 29 to 92 per cent in patients who die of tuberculosis.[22] The human variety of tubercle bacilli, swallowed in infected sputum, is responsible for the majority of tuberculous infections of the intestines. Although patients with far-advanced tuberculosis have a greater incidence, minimal pulmonary tuberculosis does not preclude the possibility of intestinal tuberculosis. The extent of involvement varies from a local productive reaction to marked ulceration of a large portion of the bowel. Although any portion of the intestines may be involved, the most common site is the ileocecal junction. The marked improvement in one of our patients who received streptomycin and PAS suggests that this form of treatment is of value during pregnancy.

Miliary Tuberculosis

The history of this 25-year-old white primigravida is abstracted because of its interesting aspects.

In the second month of gestation, in September, 1950, routine chest x-ray revealed pulmonary tuberculosis with cavitation in the right upper lobe. Pneumothorax was instituted at this time and the patient appeared to be improving clinically although x-rays did

not show a regression of the lesions. In the ninth month of pregnancy she developed chills, sweating, nausea, and fever up to 40° C., and one week later she had a low forceps delivery of a living male child that weighed 2,670 grams.

Following delivery her abdominal symptoms persisted and an exploratory laparotomy was done three weeks post partum which revealed a large liver, the site of miliary tuberculosis, miliary tuberculosis of the appendix, which was removed, and generalized miliary tuberculosis of the peritoneum. She was placed on dihydrostreptomycin, receiving 1 to 2 Gm. daily for 6 weeks following which she received 1 Gm. twice a week for several months. The pneumothorax was continued and the patient was discharged improved twelve weeks post partum. Follow-up for two years has shown her tuberculosis to be inactive and both she and her infant are in good health.

Comment.—Spencer[23] states that the combination of miliary tuberculosis and pregnancy must be unusual and he was unable to find a case in the recent literature up to 1950. He reported a case in which spontaneous delivery of a living infant occurred with temporary recovery of the mother from miliary tuberculosis but death shortly thereafter from tuberculous meningitis and pyelonephritis. Silverman and Feinblatt[24] in 1948 reported a case of miliary tuberculosis with the development of tuberculous meningitis in the second trimester of pregnancy. The patient received a total of 315 Gm. of streptomycin intramuscularly and 15 Gm. intrathecally and delivered a normal infant shortly before term. Follow-up 8 months post partum revealed both mother and infant to be living and well.

Tuberculous Pericarditis

The patient who had tuberculosis of the pericardium was first admitted to the New York Hospital in 1935 because of dyspnea, increasing orthopnia, ankle edema, shortness of breath, easy fatigability and tachycardia.

She was a 29-year-old Venezuelan woman who had had 5 normal spontaneous deliveries previously and who had been in good health up until several weeks before admission. After thorough investigation, a diagnosis of adhesive pericarditis of unknown etiology was made. The patient signed herself out of the hospital and remained at bed rest at home for 2 months. She was readmitted on June 16, 1935, in early labor and had a normal spontaneous delivery of a premature, living male infant weighing 1,540 grams in the thirty-fourth week of gestation.

On returning home she was unable to carry out normal household activities because of dyspnea, shortness of breath, and weakness, and was readmitted to the hospital. In 1936 a partial pericardectomy was performed and a tuberculoma of the pericardium removed. No evidence of tuberculosis elsewhere in the body could be discovered. Following this procedure she was much improved and was able to carry on her activities. She was readmitted to the hospital in 1937 because of amenorrhea of 3 months' duration. Following medical, cardiological, and obstetrical consultation, a therapeutic abortion was decided upon and in December, 1937, an abdominal hysterotomy and tubal ligation were performed. Frequent follow-up to 1952 has revealed her to be in good health.

Comment.—The most frequent route of infection in tuberculous pericarditis is from caseous mediastinal lymph nodes, and, less frequently, by extension from pleura or lung; the least frequent route is by hematogenous seedings.[25] Until recently it was generally a fatal complication of tuberculosis and occurred usually in Negroes.[26] Recently there have been case reports of the successful use of streptomycin in pericardial tuberculosis and this is now considered the treatment

of choice.[26-28] Our case is most unusual in that recovery occurred long before the advent of modern drugs. In retrospect the therapeutic abortion done in 1937 was probably unnecessary.

Summary of Obstetrical Course of All Patients

Table III shows the type of delivery for all patients with extrapulmonary tuberculosis.

TABLE III. TYPE OF DELIVERY IN EXTRAPULMONARY TUBERCULOSIS

Normal spontaneous delivery	33
Low forceps	11
Midforceps	4
Breech	2
Cesarean section	9
	59

Fifty of the 59 deliveries, or 83 per cent, terminated vaginally and 9 of the deliveries were by cesarean section. Two of the 3 sections done on patients with osseous tuberculosis were for obstetrical indications and the third was done in a patient who had a hip fusion in whom vaginal delivery was thought not feasible because of mechanical difficulties. One of the 4 sections done in patients with renal disease was for an obstetrical indication and 3 were for renal tuberculosis. Two sections were done in one patient with intestinal tuberculosis who had extensive perineal and anal tuberculous fistulas. The indications for 6 of the 9 sections performed were extrapulmonary tuberculosis, giving an incidence of 10 per cent. It is unlikely that the patient with the fusion of the hip or the 3 patients with renal tuberculosis would be delivered by section at the present time.

Analgesia

Table IV shows the types of analgesia used.

TABLE IV. ANALGESIA IN EXTRAPULMONARY TUBERCULOSIS AND PREGNANCY

Morphine sulfate	32
Meperidine	21
Other	3
None	3
	59

Morphine sulfate was used in the early years of this analysis when it was the usual routine for obstetrical analgesia. In more recent years meperidine has been used. No untoward effects were noted from the analgesics used since the lungs were not actually involved in the tuberculous process.

Anesthesia

Table V gives the anesthetic agents employed at delivery.

Nineteen of the 59 deliveries were done under local and pudendal block which is in line with our policy of using local anesthesia whenever feasible. No apparent ill effects resulted from either or nitrous oxide in the patients on whom it was used.

TABLE V. ANESTHESIA IN EXTRAPULMONARY TUBERCULOSIS AND PREGNANCY

Vaginal Delivery.—	
Gas, oxygen, ether	28
Local	12
Nitrous oxide	5
None	4
Caudal	1
Cesarean Section.—	
Local	7
Gas, oxygen, ether	2
	59

Infants

Fifty-six of the 59 deliveries resulted in 57 liveborn infants. There was one set of twins. In the three infants who died, the tuberculosis did not play a role; one infant had erythroblastosis, one infant was macerated at birth, and one infant died of prematurity following premature separation of the placenta in the mother.

TABLE VI. WEIGHTS OF INFANTS BORN OF MOTHERS WITH EXTRAPULMONARY TUBERCULOSIS

1,500-1,999 grams	3
2,000-2,499 grams	2
2,500-2,999 grams	13
3,000-3,499 grams	24
3,500-3,999 grams	11
4,000-4,999 grams	7
	60

Fifty-five of the 60 infants, or 92 per cent, weighed 2,500 grams or over at birth, compared to 93 per cent for all infants born at the Lying-In during this period who weighed 2,500 grams or over.

Follow-Up

The duration of follow-up in the 45 patients is shown in Table VII.

TABLE VII. DURATION OF FOLLOW-UP

Up to 3 months	3
3 to 12 months	6
1 to 5 years	21
6 to 10 years	9
11 to 20 years	6
	45

Only 3 patients were followed less than 3 months after delivery and an additional 6 patients were not followed longer than one year. The large majority of the patients, 36 of the 45, were followed for 1 to 20 years after delivery.

Results

None of the 45 patients died or showed progression of the disease following delivery. Thirty-nine showed no change in their condition and 6 were

improved. Improvement occurred in 2 patients who had nephrectomies performed in the last trimester of pregnancy. The other 4 patients who improved all received streptomycin and PAS.

The first patient had a nephrectomy performed 3 weeks post partum and received streptomycin and PAS preoperatively as well as for 3 months postoperatively.

The second patient had lymph node tuberculosis and minimal active pulmonary tuberculosis. She received streptomycin and PAS for 3 weeks post partum with improvement of both the pulmonary and cervical node lesions.

The third patient had intestinal tuberculosis and tuberculous fistulas of the perineal and anal regions. She received streptomycin and PAS for one month with improvement in her condition.

The fourth patient developed miliary tuberculosis in the ninth month of gestation and received streptomycin and PAS for several months postpartum. Both the pulmonary and miliary lesions improved.

Streptomycin was used in one other patient who had a nephrectomy for renal tuberculosis 9 years before delivery. She was given streptomycin and PAS for 6 weeks before and for 2 months after cesarean section. Her condition remained good.

Streptomycin and PAS were used in 5 patients in our series with excellent results. The large majority of the patients were delivered before streptomycin was available for use and in most of the patients delivered recently it was not thought to be indicated because of the long period of inactivity of the tuberculous lesions.

Summary

Extrapulmonary tuberculosis is an infrequent complication of pregnancy (0.1 per cent at the New York Lying-In Hospital). Usually the original site of inoculation has healed and only the extrapulmonary focus remains so that pulmonary tuberculosis is seldom a factor in the prognosis. The osseous and renal systems were most frequently involved in our patients, 21 and 18 times, respectively. The lymph nodes were the site of tuberculosis in 9 patients, the intestines in 3, and miliary, peritoneal, and pericardial tuberculosis each occurred once.

No operative procedures were performed during pregnancy in the patients with osseous tuberculosis. Conception occurred on an average of 17 years after the onset of the skeletal tuberculosis so that these patients had no active lesions. In the patients with renal tuberculosis, nephrectomy was performed on an average of 5 years before conception in 9 patients, during the seventh month of gestation in 2 patients, and 3 weeks post partum in 2 patients. Case reports in the literature substantiate the opinion that pregnancy is not a contraindication to nephrectomy for tuberculosis. Streptomycin and para-aminosalicylic acid should be used pre- and postoperatively. At present these drugs are not considered a substitute for surgical treatment.

The cervical lymph nodes are the most commonly involved in tuberculosis and were the site of the disease in all 9 of our patients. In 2 patients excision

was performed during gestation. Lymph node tuberculosis occurring during pregnancy should be treated as in the nonpregnant patient with application of the same principles as apply to surgical eradication of tuberculosis elsewhere in the body. Streptomycin and PAS are valuable additions to surgical therapy in tuberculous lymphadenitis.

Intestinal tuberculosis occurred in 3 patients, each of whom had two pregnancies. Streptomycin and PAS were available for use in only one patient, who also had anal and perineal tuberculous sinuses, and this patient's condition improved following delivery. It is suggested that streptomycin and PAS be used in the pregnant patient with intestinal tuberculosis.

One patient developed miliary tuberculosis while being treated with pneumothorax for pulmonary tuberculosis during pregnancy. A normal infant was delivered and the patient responded to streptomycin and PAS post partum. One patient had tuberculosis of the pericardium and delivered a premature infant. She subsequently had a partial pericardectomy and improved.

Analgesia and anesthesia in pregnant patients with nonpulmonary tuberculosis is not as much of a factor as in pulmonary tuberculosis. No apparent ill effects resulted from the use of morphine in our patients in 32 instances. Ether was used at 28 deliveries without ill effect. Normal spontaneous delivery occurred 33 times, low forceps were used 11 times, midforceps on 4 occasions, and there were 2 breech deliveries. Cesarean section was performed on 9 occasions but nonpulmonary tuberculosis was the indication in only 6 instances. Although 3 sections were done for renal tuberculosis, we would not do sections for this condition at present and believe that nonpulmonary tuberculosis per se is not an indication for cesarean section.

The results in the 45 patients who had full-term or premature deliveries, 93 per cent of whom were followed for 3 months to 20 years, were uniformly good. Thirty-nine showed no change in their condition and 6 patients were improved. Two of the latter group had nephrectomies performed during pregnancy and 4 received streptomycin and para-aminosalicylic acid either during pregnancy or immediately post partum.

Conclusions

1. Extropulmonary tuberculosis is not unfavorably affected by pregnancy.
2. The osseous and renal systems were most frequently involved in our patients.
3. Vaginal delivery is a safe method of delivery for patients with extrapulmonary tuberculosis. Cesarean section is not indicated except for obstetrical causes.
4. The infants born of mothers with extrapulmonary tuberculosis were normal and of average weight.
5. The antituberculosis drugs are not contraindicated in pregnancy associated with extrapulmonary tuberculosis.
6. Therapeutic abortion does not appear to be necessary in patients with extrapulmonary tuberculosis.

References

1. Ornstein, G. G., and Ulmar, D.: In Goldberg, Benjamin, editor: Clinical Tuberculosis, ed. 3, Philadelphia, 1942, F. A. Davis Company, vol. 2, chap. 30.
2. Schaefer, G., Douglas, R. G., and Dreishpoon, I. H.: Obst. & Gynec. 1: 245, 1953.
3. Cooper, D. A.: M. Clin. North America 29: 1454, 1945.
4. Wilkinson, M. C.: J. Bone & Joint Surg. 32-B: 307, 1950.
5. Gibson, G. B.: J. Obst. & Gynaec. Brit. Emp. 57: 969, 1950.
6. Bickel, W. H., Young, H. H., Pfuetze, K. H., and Norley, T.: J. A. M. A. 139: 682, 1948.
7. Bosworth, D. M., Della Pietra, A., and Farrell, R. F.: J. Bone & Joint Surg. 32-A: 103, 1950.
8. Bosworth, D. M., Wright, H. A., and Fielding, J. W.: J. Bone & Joint Surg. 34-A: 761, 1952.
9. Cibert, J., Gayet, R., and Mafart, Y.: J. d'urol. 52: 62, 1944.
10. Pugh, Winfield Scott: J. Urol. 2: 160, 1936.
11. Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, 1937, W. B. Saunders Company, vol. 2, p. 562.
12. Stevens, W. E.: Surg., Gynec. & Obst. 39: 750, 1924.
13. Lissack, E.: Am. J. Obst. & Gynec. 39: 854, 1940.
14. Falls, F. H.: In Goldberg, Benjamin, editor: Clinical Tuberculosis, Philadelphia, 1942, F. A. Davis Company, vol. 2, chap. 40.
15. Faugere, G., and Freour, G.: Rev. franç. gynec. 45: 72, 1950.
16. Kistner, R.: Am. J. Obst. & Gynec. 60: 421, 1950.
17. Watson, E. H., and Stow, R. M.: J. A. M. A. 137: 1599, 1948.
18. Nesbit, R. M., and Bohne, A. W.: J. Urol. 60: 532, 1948.
19. Pfeutze, K. H., Hinshaw, H. C., and Feldman, W. H.: In Hayes, E. W.: Fundamentals of Tuberculosis and Its Complications, Springfield, Ill., 1949, Charles C Thomas, chap. 12.
20. Greenberger, M. E., Greenberger, A. J., Klein, M., and Turell, M.: New York J. Med. 52: 1041, 1952.
21. Lester, C. W.: Am. Rev. Tuberc. 64: 691, 1951.
22. Hoon, J. R., Dockerty, M. B., and Pemberton, J. deJ.: Surg., Gynec. & Obst. 9: 417, 1950.
23. Spencer, G. E., Spino, P. D., and Silverman, J. D.: Am. Rev. Tuberc. 62: 209, 1950.
24. Silverman, E. G., and Feinblatt, T. M.: New York State J. Med. 48: 2280, 1948.
25. Johnson, R. P., and Bercu, B. A.: Am. Rev. Tuberc. 59: 656, 1949.
26. Kreinin, S., and Cooley, J. A.: Am. Rev. Tuberc. 59: 650, 1949.
27. Coe, R. P. K.: Brit. M. J. 1: 18, 1951.
28. Lewin, N., and Aronoff, A.: Canad. M. A. J. 63: 70, 1950.

530 East 70th Street
New York, N. Y.

URETHRAL DIVERTICULA IN THE FEMALE: REVIEW OF THE SUBJECT AND INTRODUCTION OF A DIFFERENT SURGICAL APPROACH

C. Richard A. Gilbert, M.D., and Francisco José Rivera Cintrón, M.D.,
Santurce, Puerto Rico

(From the Department of Obstetrics and Gynecology, University of Puerto Rico School of Medicine, School of Tropical Medicine and the San Juan Municipal Hospital)

THE discussion of diverticula of the female urethra is overlooked in the curriculums of most medical schools. This is supported by 50 consecutive inquiries into the teaching programs in urology and gynecology in the United States. As a corollary, few general practitioners diagnose or even suspect this disease entity. Kearns, under the direction of Wharton,[1] pointed out that even the gynecological or urological specialist may not be making the diagnosis with frequency, for from 1890 to 1940 there were only 30 cases noticed at the Johns Hopkins Hospital. Furthermore, Higgins and Roen[2] report that only 7 cases were seen at the Cleveland Clinic in 22 years and Cook and Pool[3] report 71 cases from the files of the Mayo Clinic as of 1948.

It is the purpose of this presentation to point out that urethral diverticula are moderately frequent and when infected become an important disease entity, to review the subject and present new information in regard to signs, symptoms, diagnosis, and surgical approach, with the hope that interest will be stimulated in placing greater emphasis on the subject in medical schools.

Comment

Moore[4] aptly states that urethral diverticula are found in direct proportion to the avidity with which they are sought and supports the statement by reporting 10 cases from his files. On July 15, 1950, Carson[5, 6] stated before the Urological Association of Puerto Rico, "in 11 years our local hospital had 35,000 admissions and only 1 case of urethral diverticulum. From 3 nearby hospitals, 1 case was noted in 60,718 admissions since 1945. In October, 1949, a paper on the subject was presented by Dr. O. M. Caplan of Miami and within the succeeding 4 months 4 cases were referred for urological treatment." He further expressed interest in the effect that the presentation of his paper would have upon the frequency with which the disease would be discovered subsequently in Puerto Rico. The only case of urethral diverticulum on record at the San Juan Municipal Hospital, where there are 10,900 yearly admissions, was diagnosed Aug. 9, 1950, or just 3 weeks after Dr. Carson presented his paper.

Johnson[7] reports a similar experience and states that up to 1936, at the University of California, 2 cases of urethral diverticulum were recorded and

in another hospital having 140,000 admissions in 10 years the diagnosis was not made. Yet, after 2 cases were demonstrated to the physicians working in urology, 9 additional cases were found in 1 year.

Our experience is in keeping with that of the above authors. A urethral diverticulum was demonstrated to the staff of the Ryder Memorial Hospital, Puerto Rico. Three months later one of the staff members diagnosed a similar case. These are the only urethral diverticula on record at that hospital.

In February, 1953, a case history was presented to the staff at the Ramey Air Force Base, Aguadilla, Puerto Rico. In April, 1953, or just 1 month later, a diagnosis of urethral diverticulum was made. This is the only record of a urethral diverticulum at that hospital. (In both hospitals, the medical staffs are composed entirely of graduates from medical schools in the United States.)

At variance with the infrequency with which urethral diverticula are noted at most institutions, certain investigators find the disorder on numerous occasions. There are numerous case reports in the literature.[11-37, 98, 99, 100, 103] Taylor[8] reported 23 cases in 1948 and saw 7 additional cases within a brief 18 month period. Leckie[9] reports 8 cases in 1 hospital in Detroit in 22 months. Carson[6] saw 5 cases from 1948 until July 15, 1950; one of us (C. R. A. G.) has seen 8 cases within an 11 month period, and Bergman[10] reports finding 7 cases within 2 weeks.

Examination of the case histories reveals that it is usual for a patient to attend a large number of physicians before a diagnosis of urethral diverticulum is considered. It is obvious that many physicians are not "diverticulum conscious." At the risk of belaboring a point, we feel this is due to the terse fashion in which the subject is presented in many institutions of medical instruction.

Etiology

The etiology of the urethral diverticulum is unknown but presents 2 possibilities, congenital and acquired; each possibility is championed by many.[38-44] Higgins and Rambousek[46] believe that 11 of their 12 cases were acquired and Larroude and Latorre[47] and many others write of acquired diverticula of the urethra.[17, 45, 95] Various authors[45, 97] have suggested that urethral diverticulum may be acquired as a result of trauma incidental to instrumentation of the urethra, urethral stone, or deep electrocoagulation of urethral lesions; nor is it inconceivable that intramural infection and abscess formation could be an etiological factor.

In not a single case was urethral diverticulum noted in the nullipara and symptoms of the infected urethral diverticulum were frequently initiated after the first delivery. In one-half of the patients in whom the history of their labor was reliable, labor was prolonged or delivery by forceps difficult (Table I). This would lend credence to the suspicion of trauma of the urethra incidental to parturition as a more frequent cause. However, the diverticulum may have been present in each case prior to delivery; following parturition

recognition was facilitated because of exacerbation of the symptoms by infection. That the latter may be the true course of events is suggested by the history in one patient of a short labor and uncomplicated delivery followed by acute urinary retention (possibly secondary to saddle block anesthesia). This complication was treated by repeated catheterization of the bladder with resultant infection of the lower urinary tract and in all probability infection of a pre-existent diverticulum of the urethra.

TABLE I. SUMMARY OF THE OUTSTANDING FEATURES OF URETHRAL DIVERTICULA IN EIGHT PATIENTS

	NO. OF PATIENTS
Nulligravida	0
Multigravidas	8
Chief complaint initiated immediately following the first delivery	4*
Prolonged labor or "difficult" forceps	3 (2 other patients did not accurately recall the length of labor)
Average age of the patients at the onset of symptoms	25* years
Average number of physicians seen by the patient before the correct diagnosis was made	9.5*
Chief complaint dyspareunia	7*
Many of the symptoms were those resulting from infection of the lower urinary tract	2
Many of the symptoms were those resulting from infection of the upper and lower urinary tract	6
Failure to respond to repeated antibiotic therapy	7*
Hematuria	2
Suburethral mass	7
Tenderness over the anterior vaginal wall	8
Pus expressed by "stripping" the urethra with the examining finger	4
Ostium of the diverticulum visualized through the panendoscope	5
Diagnosed by x-ray findings after inability to locate the diverticulum	1
Recurrence of diverticulum after surgery	0
Urethrovaginal fistula after surgery	0

*One of the 8 patients was not considered because she had an ovarian neoplasm in addition to diverticulum of the urethra.

Congenital diverticula are not frequently found, but have been reported.[38, 50, 51, 80, 94] Johnson[7] reported 1 in a neonatal infant and Higgins and Rambousek[46] in 1945 found 2 cases reported in the literature. Huffman's[48] excellent presentation of the embryology and development of periurethral glands in the human female leaves little doubt of the possible congenital origin of some of these diverticula. In 1911 Grubenman quoted by Felix[49] stated, "the irregular form of the wall of the sinus urogenitalis gives opportunity for the formation of diverticula." However, the literature presents contradictory conclusions concerning the existence of paraurethral ducts and glands and their situation in the urethra. It may be concluded that there are occasional glands and ducts along the female urethra, for anatomical studies show the presence of cysts in the paraurethral tissues often clearly connected with the urethra by paraurethral ducts.[1] Ercole[50] in 1947 and Lacal[51] in 1948 presented papers on congenital diverticula. The incidence of the congenital

variety could be determined by the pathologist who would inject dye into the urethra of each infant coming to autopsy and subsequently search meticulously for diverticula. Furthermore, the histological structure could be recorded accurately.

Dysontogenetic diverticula of the urethra are known to occur in the form of ectopic ureters.[4, 52, 61]

Pathology

The pathology of the wall of the sac in the cases presented was typically that of a chronic abscess. If the diverticula were congenital in origin one would expect the lining to be similar to that of the urethra, i.e., stratified squamous or transitional epithelium. In each of the cases referred to in Table I, the lining could readily have been destroyed by infection and pressure. Wharton and Kearns[1] reported the lining of a urethral diverticulum completely intact and reported others in which part of the lining was present as cuboidal or squamous epithelium. Rashbaum and Seley[53] were fortunate in finding 16 cases in which the lining of the diverticulum was made up of either squamous, columnar, cuboidal, transitional, or stratified squamous epithelium and only 8 of their cases had a granulation or fibrous tissue lining.

Bacteriology

The literature does not record which organism most frequently infects diverticula of the urethra. In 4 of the cases given in Table I, cultures were taken and revealed *B. coli.*

Location and Size of the Diverticula

The location of the ostia and size of the 8 diverticula recently seen were as follows: In No. 1 it opened into the posterior urethra just to the right of the midline approximately 1 cm. from the internal urethral orifice. The diameter of the sac was 3 cm.

In No. 2 it opened into the posterior portion of the urethra in the midline just distal to the internal urethral meatus. The diameter of the sac was 6 cm. and it surrounded the urethra on either side. It also extended over the posterior inferior surface of the bladder.

In No. 3 the diverticulum opened in the midline 3 cm. from the internal urinary meatus. The diameter was 3 cm. and the diverticulum had fingerlike projections branching from the main sac.

In No. 4 it opened into the anterior portion of the urethra in the midline 1 cm. from the internal urethral meatus; the diameter was 5 cm. The sac extended from the anterior of the urethra to surround it and also extended posteriorly on either side of the urethra.

In No. 5 the ostium opened into the middle third of the urethra. The diameter was not given but the mass was described the size of a pea and also as the size of a cherry.

In Nos. 6, 7, and 8 the openings were into the posterior portion of the lower third of the urethra in the midline. The diameter of the sac was about 2.5 cm. in each case.

Other investigators[1, 5, 6, 54] have reported the size to vary from 3 to 8 cm. in diameter and certain ones to be still larger, extending the entire length of the urethra, beneath the trigone, and surrounding the urethra.

In the cases reported by Wharton and Kearns[1] the sites were as follows: anterior third of the urethra, 4 cases, middle third of the urethra, 9 cases, and posterior third, 8 cases. All opened into the vaginal half of the urethral circumference. In one of their cases there were 2 diverticula of the urethra and in one case there was an associated diverticulum of the renal pelvis. Trafton[55] and also Counseller[56] believe the usual site of the ostium to be the middle third of the urethra and in the midline.

The age of the patients at the time of the onset of symptoms in this series is 15, 19, 30, 23, 28, 32, and 25 years (Table I). Wharton and Kearns[1] also found only adults in their series. Menville and Mitchell,[57] in a review of 80 cases, report an average age incidence of 38.8 years. It is probable that the age at which symptoms first appeared was much earlier. Johnson reports 1 case in an infant shortly after birth.

Diagnosis Including Symptoms and Signs

The diagnosis of infected urethral diverticulum should be considered whenever infection of the urinary tract fails to respond to or recurs after adequate and appropriate antibiotic therapy. This becomes especially ominous when adequate study fails to reveal a lesion in the kidneys, ureters, or bladder to account for persistent pyuria. Due to the fact that cystitis often results and pyelitis occasionally results from secondary infection from an infected urethral diverticulum, the patient may complain of costovertebral-angle pain with or without radiation over the course of the ureter, chills, fever, nocturia, frequency, dysuria, and pyuria. Dyspareunia is almost always present and is the most important symptom (Table I). The history of these symptoms following parturition is especially significant (Table I). After standing for a long period the patient may complain of vaginal pain or dribbling of urine or pus; she may also complain of pain on sitting.[58, 93] A rare patient may complain of acute urinary obstruction; terminal hematuria or pyuria is occasionally present. There is often temporary relief after purulent discharge; stranguria and urosepsis are frequent.

Enuresis in small children, the feeling that the bladder was not empty after micturition, and pain in the pelvis, thighs, and lumbar regions, are symptoms recorded by other authors[5, 6, 53, 54, 59, 60] but were not noted in our patients.

When the diverticulum is located in the proximal third of the urethra there may be tenderness on deep pressure with the finger tips over the symphysis pubis and there may be tenderness radiating to the anterior vagina when the cervix is moved, thus making it possible to confuse the diagnosis with pelvic inflammatory disease. On vaginal examination there is marked tenderness over the anterior vaginal wall. When the diverticulum is located in the distal two-thirds of the urethra a pultaceous mass is usually palpable

but if located near the internal urethral orifice the mass may feel so like the bladder as to be indistinguishable from it. When the orifice of the diverticulum is large the mass may vanish under pressure from the examining finger. In this case pus or urine will be noted to pour from the external urethral orifice, especially if the urethra is "stripped" toward the external urinary meatus with the index finger.[104] If the mass cannot be located at the first examination it is often prominent when the patient returns 1 week later, if she has refrained from sexual intercourse or vaginal douching during the interim. When the orifice of the diverticulum is very small, stripping of the urethra fails to express pus. Even if a mass cannot be palpated, the urethra is carefully examined with the panendoscope. When the orifice to the diverticulum is of pin-point size it may be located only with the greatest difficulty. With the panendoscope within the urethra the index finger of the gloved left hand is inserted into the vagina so that the index finger and the tip of the panendoscope are approximated at the internal urethral orifice. The index finger is oscillated against the urethra and follows the tip of the panendoscope as it is slowly withdrawn. During this maneuver jets of pus cells will be forced through even a diminutive ostium into the urethra. The cloud of pus can readily be seen through the panendoscope and the orifice located. Once located, a ureteral catheter should be deflected into the diverticulum if possible and it may be made to curl into the diverticulum. A sterile needle and syringe are then attached to the opposite end of the ureteral catheter and pus is aspirated, cultured, and antibiotic sensitivity tests performed upon the infecting organisms. A radiopaque contrast medium (Diodrast) is then injected through the catheter until the diverticulum is filled. This procedure may reveal an ectopic ureter entering into the urethra. Anterior-posterior and lateral x-ray films are taken. If the orifice of the diverticulum cannot be located after careful examination with the panendoscope, recourse is made to urethrography according to the method described by Taylor.[8]

Briefly, a silk ligature is placed distal to the bulb of a No. 20F Foley catheter and an orifice is cut immediately proximal to the bulb. After the catheter is introduced through the urethra into the bladder the bulb is distended and pulled snugly against the sphincter. After the air is forced from the catheter the external urethral meatus is pinched about the catheter and the urethra is filled with Diodrast. Allis forceps may be used to hold the external urethral meatus snugly against the stem of the catheter. X-rays are taken in the anterior-posterior and lateral direction. Young[83] also describes the x-ray findings diagnostic of urethral diverticulum.

Carson[5, 6] states that if the orifice to the urethral diverticulum is large a No. 16 French pandendoscope sheath may be passed into the diverticulum. This was not done in the cases given in Table I but it may be of value in exposing adenocarcinoma within the diverticulum. The frequency of adenocarcinoma within urethral diverticula is unknown but both this complication and mucosal hyperkeratosis within the sac have been reported.[63, 64] A more frequent complication within the urethral diverticulum is calculus. The

diverticulum in only 1 of the cases in Table I contained a stone. However, in the literature there are many such case reports.[1, 2, 52, 69, 70, 72-74, 77, 78, 92, 96, 102] In the study at Johns Hopkins Hospital,[1] 10 per cent of the diverticula contained stones and one diverticulum contained 17 stones. Others also report finding multiple calculi in diverticula.[33, 67, 68, 84] Certainly if a calculus is present within the diverticulum it facilitates recognition.

Spontaneous rupture of the sac and subsequent fistula formation have been reported. Lithiasis of the fistulous tract has also been reported.[86]

Differential Diagnosis

The following should be included in differential diagnosis:

1. Gartner's duct cyst. This cyst does not originate from the midline, is rarely infected, and is therefore not tender. There is, of course, no connection with the urethra.

2. Bladder diverticula. It is necessary to differentiate diverticula of the upper portion of the urethra from diverticula of the bladder; this can be done by urethroscopy, cystoscopy, and various roentgen procedures.

3. Ectopic ureter entering into the urethra, which has been reported by both Moore[4] and Willmarth.[61] Whenever possible, it is mandatory to insert a ureteral catheter into the supposed urethral diverticulum, outline the sac with radiopaque medium, and record the findings by radiograph. It would indeed be a catastrophe to mistake a ureter opening into the urethra for a true urethral diverticulum and transect and ligate that ureter!

4. Abscess of Skene's glands. Due to the location and consequent facile visualization of the infected Skene's glands and ducts, the differential diagnosis is rendered without difficulty.

5. Pelvic inflammatory disease. Tenderness on motion of the cervix is a frequent concomitant of infected urethral diverticula and of course is also a prominent feature of pelvic inflammatory disease. A careful pelvic examination is helpful in the differential diagnosis of the two conditions.

6. Endometriosis. Endometrial implants in the urethral area may cause momentary confusion with a urethral diverticulum containing a stone. The method of differentiating the two is obvious.

7. Gonorrheal urethritis of course responds rapidly to modern antibiotic therapy. Liu[62] cultured gonococci from a diverticulum.

8. Urinary tract tuberculosis. Any patient continuing to have pyuria after adequate antibiotic therapy should be investigated for possible urinary tract tuberculosis or diverticula at any position in the urinary tract.

9. Myoma, fibroma, sarcoma, carcinoma, etc., may momentarily be confused with diverticula of the urethra. Differential diagnosis is obvious. Hamilton and Leach[63] have reported adenocarcinoma in a previous diverticulum of the urethra.

10. Suburethral varicosities. On rare occasions a group of suburethral varicose veins may be mistaken for the sac of a urethral diverticulum. These varicosities are usually located 2 cm. from the external urinary meatus and are most often seen during pregnancy.

Treatment

The complete removal of the diverticulum sac is of secondary importance to the single basic surgical principle in preventing recurrence of the diverticulum, i.e., closure of the orifice of the diverticulum at its entrance into the urethra. This is readily accomplished if the orifice of the diverticulum enters the distal third of the urethra.

Treatment of Diverticula of the Distal Third of the Urethra.—

An incision is made through the vaginal mucosa 1 cm. from the external urethral meatus and extending for a distance of 4 cm. toward the cervix. An inverted T-shaped incision with the bar of the T at the point of the incision nearest the cervix can be made to increase exposure. Allis clamps are placed on the vaginal mucosa on either side of the incision and the pubocervicovesical fascia is dissected from the vaginal mucosa laterally as far as possible on either side. The diverticulum protrudes into the incision and the sac can be dissected free by blunt and sharp dissection and finally severed at the point of entry into the urethra.

Three principal difficulties may be encountered:

1. If the orifice of the diverticulum entering into the urethra is large, the sac of the diverticulum collapses when it is manipulated and its outlines are indistinguishable from the surrounding tissue.

2. During dissection, the sac of the diverticulum may be ruptured with resultant collapse of the sac.

3. Occasionally the point of entry of the diverticulum into the urethra is not noticed and a large portion of the posterior urethral wall is removed with the diverticulum sac. This is especially prone to happen if the diverticulum extends for some distance along the posterior portion of the urethra. To circumvent these difficulties a number of ingenious devices have been contrived, the most generally useful being that described by Moore.[4] In this technique a stab wound is deliberately made into the belly of the urethral diverticulum. A bag of a No. 16 Foley catheter, whose tip has previously been cut off, is inserted through the stab wound and a purse-string suture, placed in the tissue surrounding the catheter, is tied, thus securing the bag of the catheter in the diverticulum. The bag of the catheter is distended and traction is made on the catheter in the direction of the vaginal orifice, thus making the sac more readily outlined and accessible.

On rare occasions the sac of the diverticulum is not confined to the posterior urethra but surrounds the urethra, extending anteriorly. In this case it becomes necessary to open the sac of the diverticulum, close the diverticular orifice which opens into the urethra, and dissect as much of the sac free as possible. All of the sac may not be removed under these conditions. Although Higgins and Rambousek[46] state that if the entire sac of the diverticulum is not removed recurrence is inevitable, it has been our experience that, if the orifice of the diverticulum entering into the urethra is properly closed, no recurrence is to be expected. Furniss[88] advocated electrocoagulation of the mucosa. This was not done in any of the cases presented.

Treatment of Diverticula Opening into the Posterior Portion of the Proximal Third of the Urethra.—

When the ostium of the diverticulum enters into the posterior urethra near the internal urethral orifice it is helpful to introduce a Foley catheter into the bladder through the urethra. The outline of the catheter in the urethra can be palpated during operation and the location of the posterior wall of the urethra easily determined.[57] The distended bag of the Foley catheter, when snugly pulled against the internal urethral meatus, can be palpated and is especially helpful as a landmark when dissecting free a large urethral diverticulum adjacent to the proximal urethra and trigone. Young[89] in 1938 and Cole[90] in 1949 proposed passing a sound through the urethra into the orifice of the diverticulum to facilitate transvaginal excision of the sac. On occasions a ureteral catheter placed through the ostium and curled into the sac of the diverticulum helps to outline the sac and reveals the position of the ostium of the diverticulum.[3] Methylene blue can be injected into the sac so that the lining is more readily recognizable when the sac is opened. The objection to this procedure is that the dye frequently pours from the external urethral orifice and stains the tissue in the operative field. Dr. Frank Kaltreider has considered filling the diverticulum through a ureteral catheter with a plastic substance, allowing the plastic to harden prior to surgery. In the same trend, Hyams and Hyams[91] advised packing the sac transurethrally with a strip of gauze, thus converting it into a semi-solid tumor, facilitating its dissection and accurate excision.

Treatment of Diverticula Opening into the Anterior Portion of the Proximal Third of the Urethra.—

When the orifice of the diverticulum opens into the anterior portion of the urethra, exposure becomes increasingly difficult the closer the ostium approximates the external urinary meatus. Exposure is of paramount importance and when the ostium of the diverticulum opens into the upper anterior portion of the urethra it can best be attained from a suprapubic approach.

With the aid of the panendoscope a ureteral catheter is coiled into the diverticulum if possible. In addition a Foley catheter is introduced into the bladder through the urethra and the bag distended with fluid. A transverse suprapubic abdominal incision is made just above the symphysis pubis through the skin, fat, rectus muscles, and fascia. The anterior wall of the bladder and upper anterior surface of the urethra are readily exposed. The location of the internal urinary meatus, urethra, and urethral diverticulum is facilitated by palpation of the distended bag of the Foley catheter, the shank of the Foley catheter, and the coiled ureteral catheter, respectively. In order to outline the urethra, Cole[90] used a urethral sound instead of the Foley catheter. The diverticulum is purposely opened and the ostium connecting the urethra with the diverticulum is immediately identified by visualization of the ureteral catheter entering from the urethra.

The closure of the ostium is the crux of the entire procedure and is accomplished with sutures of No. 0000 chromic gut (atraumatic needle) placed in interrupted fashion so that tissue is picked up on either side of the urethral defect. Silk should never be used because of the danger of inadvertently placing a nonabsorbable suture within the urethral orifice resulting in subsequent calculus formation about the silk. Two additional rows of interrupted sutures are placed in such fashion that each suture when tied tends to fold the tissue toward the urethra. No drain is necessary.

When the vaginal approach has been used for diverticula entering into the posterior urethra an additional strong repair is accomplished by suturing the pubocervicovesical fascia across the repair site with interrupted sutures and, after the excess vaginal mucosa is trimmed, it is closed with a continuous suture. Carson[5, 6] suggests that suprapubic cystotomy should be done to divert urinary flow from the urethra. This would appear to be unnecessary, for a Foley catheter passed through the urethra into the bladder may be left for 5 days or longer and is much less traumatic than suprapubic cystotomy.

Postoperative Complications

1. Stress incontinence can occur following surgery for the diverticulum located in the lower urethra. In the series presented this complication has never persisted longer than 3 weeks after operation.

2. Various authors report recurrence of the diverticulum to be frequent. If the ostium leading into the urethra is adequately closed at operation, the incidence of recurrence will necessarily be low.

3. Urethrovaginal fistula occurred in two of Higgins and Rambousek's[46] five cases. If the defect in the urethra is adequately closed at operation, according to the plan outlined, fistula should not occur.

Summary

1. Evidence is presented suggesting that infected diverticula of the urethra are more frequent than is commonly suspected.

2. A table summarizing the outstanding features of urethral diverticulum in 8 patients is presented.

3. The etiology, location, size, symptoms, signs, diagnosis, differential diagnosis, and treatment of diverticula of the urethra are discussed.

4. A new surgical approach is presented to diverticula originating from the upper anterior portion of the urethra.

References

1. Wharton, L. R., and Kearns, W.: J. Urol. **63**: 1063, 1950.
2. Higgins, C. C., and Roen, P. R.: J. Urol. **49**: 715, 1943.
3. Cook, E. N., and Pool, T. L.: J. Urol. **62**: 495, 1949.
4. Moore, T. D.: J. Urol. **68**: 611, 1952.
5. Carson, R. B., and Wells, W. D.: South. M. J. **44**: 285, 1951.
6. Carson, R. B.: Bol. Asoc. méd. de Puerto Rico **42**: 475, 1950.
7. Johnson, C. M.: J. Urol. **39**: 506, 1938.
8. Taylor, W. N.: Urologists' Correspondence Club letter **16**: 37, 1950.
9. Leckie, G.: Harper Hosp. Bull. **5**: 139, 1947.
10. Bergman, R. T.: Urol. & Cutan. Rev. **53**: 590, 1949.

11. Bolivar Drummond, J.: Rev. de ginec. e d'obst. **2**: 242, 1942.
12. Rocchi, A., Alvarez Vicente, A., and Llorens, J. L.: Rev. argent. urol. **18**: 151, 1949.
13. Tauber, R.: Urol. & Cutan. Rev. **51**: 511, 1947.
14. de Surra Canard, R., & Irazu, J.: Rev. argent. de urol. **15**: 481, 1946.
15. Sartorio Riganti, J., and Gutierrez Beruti, E.: Rev. méd.-quir. de pat. fem. **24**: 279, 1945.
16. Downer, I. G., and Virgilio, F. D.: J. Urol. **54**: 53, 1945.
17. Ercole, R.: Rev. argent. de urol. **14**: 132, 1945.
18. Milnor, G. C.: Proc. Staff Meet. Clin., Honolulu **13**: 113, 1947.
19. Miranda, A.: Hospital, Rio de Janeiro **23**: 51, 1943.
20. Ingelman-Sundberg, A.: Nord. med. **42**: 1168, 1949.
21. Adams, A. W.: Brit. J. Urol. **21**: 152, 1949.
22. Laskey, N. F., and Hill, L. M.: Harlem Hosp. Bull. **1**: 33, 1948.
23. Parmenter, F. J.: J. Urol. **45**: 479, 1941.
24. Díaz Colodrero, A. A.: Rev. méd.-quir. de pat. fem. **16**: 387, 1940.
25. Cromer, J. K., and Belt, N.: M. Ann. District of Columbia **8**: 173, 1939.
26. Hyman, A., and Leiter, H. E.: J. Mt. Sinai Hosp. **6**: 190, 1939.
27. Dozsa, E.: Ztschr. f. urol. Chir. u. Gynäk. **44**: 78, 1938.
28. Townsend, J. M.: Urol. & Cutan. Rev. **42**: 706, 1938.
29. Plătăreanu, V., Tănăsescu, I., and Hoepfner: Bucuresti med. **10**: 61, 1938.
30. Pratt, J. P.: Urol. & Cutan. Rev. **42**: 803, 1938.
31. Schmitz, H. E.: Urol. & Cutan. Rev. **43**: 596, 1939.
32. Schmitz, H. E., and Nelson, P. A.: Am. J. Obst. & Gynec. **38**: 707, 1939.
33. Tagariello, P.: Riv. di chir. **3**: 537, 1937.
34. Rivair, J.: Zentralbl. f. Chir. **64**: 2612, 1937.
35. Lower, W. E., and Tormey, T. W., Jr.: Ann. Surg. **107**: 923, 1938.
36. Rebaudi, G.: Arch. ital. di urol. **14**: 218, 1937.
37. Foley, F. W. B.: J. A. M. A. **104**: 1314, 1935.
38. Rioseco, E., and Vargas, J.: Urol. & Cutan. Rev. **48**: 209, 1944.
39. Credídio, L., and Arra, J. E.: An. Clín. ginec. Fac. med. Univ. São Paulo, p. 128, 1947.
40. Pate, V. A., Jr., and Bunts, R. C.: J. Urol. **65**: 108, 1951.
41. Murray, E. G.: Bol. Soc. de obst. y gynec. de Buenos Aires **21**: 331, 1942.
42. Engel, W. J.: J. Urol. **45**: 703, 1941.
43. Kolbenheyes, Z.: Ztschr. f. urol. Chir. u. Gynäk. **45**: 217, 1946.
44. Fagerstrom, D. P.: J. Urol. **49**: 357, 1943.
45. Iofan, Y. M., and Smelovskiy, V. P.: Sovet khir., No. 2, p. 335, 1936.
46. Higgins, C. C., and Rambousek, E. S.: J. Urol. **53**: 732, 1945.
47. Larroude, J. B., and Latorre, B.: Día méd. **22**: 2582, 1950.
48. Huffman, J. W.: Am. J. Obst. & Gynec. **46**: 773, 1943.
49. Felix, W.: The Development of Urogenital Organs, in Keibel, Franz, and Mall: Manual of Human Embryology, Philadelphia, 1912, J. B. Lippincott Company, chap. 22, pp. 752-973.
50. Ercole, R.: Rev. argent. de urol. **16**: 103, 1947.
51. Lacal, F.: Día méd. **20**: 1223, 1948.
52. Lane, C.: Urol. & Cutan. Rev. **47**: 363, 1943.
53. Rashbaum, M., and Seley, G.: New York State J. Med. **42**: 243, 1945.
54. Scheinman, L. J.: Northwest Med. **49**: 469, 1950.
55. Trafton, H. M.: S. Clin. North America **25**: 589, 1945.
56. Counseller, V. S.: Am. J. Obst. & Gynec. **57**: 231, 1949.
57. Menville, J. G., and Mitchell, J. D., Jr.: J. Urol. **51**: 411, 1944.
58. Rodriguez Velasco, A.: Bol. Soc. chilena de obst. y ginec. **9**: 62, 1944.
59. Folsom, A. I., and O'Brien, H. A.: J. A. M. A. **128**: 408, 1945.
60. Herman, L., and Greene, L. B.: Tr. Am. A. Genito-Urin. Surgeons (1944) **37**: 297, 1945.
61. Willmarth, C. L.: J. Urol. **59**: 47, 1948.
62. Liu, Y. Y.: Chinese M. J. **66**: 280, 1948.
63. Hamilton, J. D., and Leach, W. B.: Arch. Path. **51**: 90, 1951.
64. E. and A. de la Peña: Rev. españ. cir. **2**: 10, 1945.
65. Comotto, C., Berri, H. D., and Cartelli, N.: Rev. argent. de urol. **15**: 106, 1946.
66. Brøbeck, O.: Acta radiol. **35**: 27, 1951.
67. Shafman, S. A.: Khirurgiya, No. 12, p. 154, 1937.
68. Kini, M. G.: Brit. J. Urol. **11**: 155, 1939.
69. Carter, R. G.: Urol. & Cutan. Rev. **46**: 494, 1942.
70. Anglada, E.: Vida nueva **48**: 277, 1941.
71. Seymour, G. C.: Canad. M. A. J. **45**: 410, 1941.
72. de Sousa, E., and Campos da Paz., Jr.: Rev. de gynec. e d'obst. **1**: 421, 1939.
73. Gaston, E. A., and Ferrucci, J.: New England J. Med. **221**: 379, 1939.

74. Edwards, F. D., and Deddens, L. E.: J. M. A. Georgia **28**: 449, 1939.
75. Appelgren, A.: Duodecim **55**: 633, 1939; abstr., Zentralbl. f. Gynäk. **63**: 2273, 1939.
76. Delgado, R.: Bol. Soc. de cir. de Rosario **9**: 607, 1942.
77. Machado Horta, H.: Rev. de ginec. e d'obst. **2**: 118, 1944.
78. Smith y Leal, R., and Capote Brito, B.: Rev. méd. cubana **53**: 859, 1942.
79. Harley, E. W., Jr., and Reynolds, C. J.: J. Urol. **62**: 498, 1949.
80. McMahon, S.: J. Urol. **55**: 69, 1946.
81. Labbé, P., Fisher, J., and Pettigrew, A.: Union méd. de Canada **79**: 647, 1950.
82. Cullen, T. S.: Johns Hopkins Hosp. Bull. **5**: 45, 1894.
83. Young, B. R., and McCrea, L. E.: Urol. & Cutan. Rev. **41**: 91, 1937.
84. Shivers, C. H. de T., and Cooney, C. J.: J. A. M. A. **102**: 997, 1934.
85. Hunner, G. L.: Urol. & Cutan. Rev. **42**: 336, 1938.
86. Scott, W. W., and Ekas, W. L.: Surgery **20**: 645, 1946.
87. Rütt, A.: Zentralbl. Chir. **75**: 853, 1950.
88. Furniss, H. D.: J. Urol. **33**: 498, 1935.
89. Young, H. H.: South. M. J. **31**: 1043, 1938.
90. Cole, F. R.: Am. J. Surg. **77**: 212, 1949.
91. Hyams, J. A., and Hyams, M. N.: Urol. & Cutan. Rev. **43**: 573, 1939.
92. Kirby, E. W., Jr., and Reynolds, C. J.: J. Urol. **62**: 498, 1949.
93. Rodríguez Velasco, A.: Bol. Soc. chilena de obst. y ginec. **9**: 62, 1944.
94. Temporal, A.: Arq. brasil de cir. e ortop. **8**: 88, 1940.
95. Kolbenheyer, Z.: Ztschr. f. urol. chir. u. Gynäk. **45**: 217, 1940.
96. Mitrofanov, P. P.: Vestnik khir. **56**: 118, 1938.
97. Rivoir, J.: Zentralbl. f. Chir. **64**: 2612, 1937.
98. Cone, R. E.: Urol. & Cutan. Rev. **40**: 803, 1936.
99. Hall, E. R.: Northwest Med. **35**: 379, 1936.
100. Flandrin, P., and Ferrier, L.: Bull. Soc. franç. d'urol., pp. 189-196, April 27, 1936.
101. Podleschka, K.: Zentralbl. f. Gynäk. **60**: 2258, 1936.
102. Casini, A.: Policlinico (sez. chir.) **43**: 145, 1936.
103. McNally, A.: Illinois M. J. **69**: 234, 1936.
104. Rashbaum, M.: Am. J. Surg. **82**: 360, 1951.

TREATMENT OF THE DYSMENORRHEA SYMPTOM COMPLEX. A PRELIMINARY REPORT ON THE EFFICACY OF A UTERINE "RELAXING FACTOR"

GEORGEANNA S. JONES, M.D., AND FRANK SMITH, M.D., BALTIMORE, MD.

(From the Departments of Gynecology and Medicine, Johns Hopkins Hospital and University)

DYSMENORRHEA is a symptom complex composed not only of menstrual cramps but generalized symptoms, backache, leg ache, headache, diarrhea, nausea and vomiting, and general malaise. There is a great difference of opinion as to the exact etiology of the syndrome. Most observers believe that both smooth-muscle contractions and vascular constriction are components. These are somehow related to the ovarian steroid pattern, as anovulatory menses are usually painless. Ancillary factors are also of prime importance, especially psychosomatic factors. These may be manifested as relatively mild tension states due to temporary work or living habits or may be much more serious immaturity problems. It is well recognized that it is important to control symptoms of dysmenorrhea as soon after the onset of the syndrome as possible, for it tends to become a habit pattern. The woman who has dysmenorrhea learns to look forward to her menses with dread which in itself, by creating additional tension, aggravates the condition.

There are many types of therapy available. Current concepts have been nicely summarized by Miller and Behrman.[1] Simple bed rest and heat applied to the lower abdomen have always been at times effective, but for the working adult these are frequently impractical. Analgesic drugs are acceptable therapy. However, drugs which are habit forming should certainly be avoided and all too frequently we find that only these are effective. Antispasmodics are also used and have their place in the therapeutic armamentarium. Approaching therapy from the standpoint of physiology we can prevent ovulation and thus prevent painful menses. Although theoretically this sounds quite logical, from a practical point of view it is not usually as successful as one might expect. In our experience it has been difficult to prevent ovulation repeatedly in the normally ovulating woman. Although one ovulation can be prevented rather readily, the second is often extremely difficult to suppress with either estrogens or androgens, unless the dosage given is excessive (Fig. 1). Estrogens in the required dose range are prone to disturb the menstrual rhythm and cause menorrhagia, while androgens may cause masculinization, neither of which is a desirable side effect. Operative procedures, other than the time-honored dilatation of the cervix, for this relatively minor condition are generally to be discouraged. Presacral neurectomy

is to be used only as a last resort and the results although frequently gratifying at the onset are often disappointing in the years following.[2]

With this relatively unsatisfactory armamentarium for the approach to the therapy of dysmenorrhea, a principle which would control the entire syndrome rather than single symptoms would therefore be most welcome. Hence, when an orally effective uterine relaxing factor (U.R.F.) was offered us for clinical testing on human beings it had enough points in its favor to warrant a trial.

In 1942, Falls and co-workers[3] reported the successful treatment of abortion with an aqueous extract of sow corpus luteum given intramuscularly. The active principle was therefore obviously not progesterone which is an alcohol-soluble, water-insoluble sterol. Krantz, Bryant, and Carr,[4] in an effort to clarify the physiologically active principle, investigated the action of these aqueous extracts of sow corpora lutea on the isolated guinea pig uterus in situ and demonstrated the presence of a substance which possessed the ability to diminish the tone and abolish spontaneous muscular contraction. In the further identification of this substance,[5] it became apparent that it was closely related both chemically and in its biological activity to a hormone described a number of years ago by Hisaw,[6] and designated as specific for the relaxation of the guinea pig symphysis. A chemical analysis by Felton and associates,[5] revealed that the uterine relaxing factor (U.R.F.) was, in addition to being water soluble, nondialyzable, heat stable, and destroyed by proteolytic enzymes and a variety of reducing agents. These properties seem to classify it as a protein or polypeptide.

Because of the ability of the hormone to produce uterine relaxation it seemed it might be of value in the treatment of dysmenorrhea. A report by Rezek[7] indicates that this is indeed possible. As an oral preparation is preferable to an intramuscular or intravenous one, experiments were designed to determine if there was any detectable relaxing activity in the blood serum after oral administration. Using the guinea pig as a test animal, it was found that 1 mg. of a typical sample of U.R.F. assayed 25 units per milligram, when tested by intravenous administration. The unit is "the minimal amount of substance which, when injected intravenously into the estrogenized virgin guinea pig, effects a 90 per cent reduction in the height of spontaneous contractions for a period of at least 10 minutes."[5] The same material assayed 1.25 units per milligram when given by stomach gavage. The assay of the serum of 9 women who received the hormone orally is seen in Table I. Although the blood serum of normally menstruating women not under treatment has shown consistently negative titers, the serum of pregnant women usually has shown a positive titer. These blood level experiments in both animals and human beings indicate that the preparation was absorbed orally. In testing the toxicity of the drug, as much as 10,000 units in a single dose was given to 10 men with no untoward results.[8] Two women under observation have also taken 10,000 units at one time and, although they were somewhat drowsy for several hours, no other effects were observed.

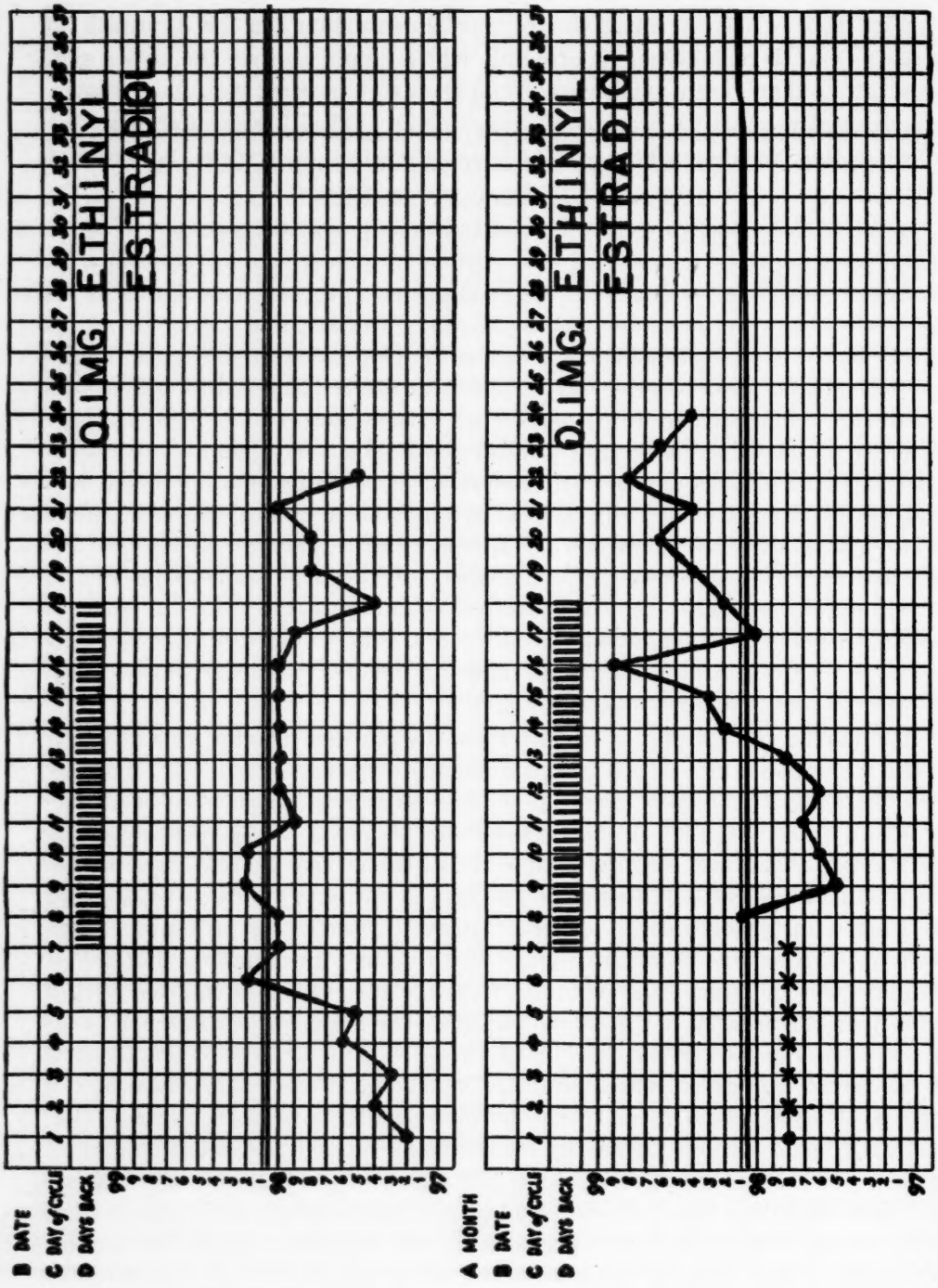


Fig. 1.—Basal temperature chart of patient receiving estrogen. Ovulation is suppressed in the first cycle but there is a rebound phenomenon and ovulation occurs in spite of continued estrogen therapy in the second cycle.

TABLE I. UTERINE RELAXING FACTOR IN HUMAN SERUM AFTER ORAL ADMINISTRATION OF LUTREXIN

PATIENTS	CONTROL PERIOD* U.R.F./C.C. SERUM	UNITS LUTREXIN GIVEN	TEST PERIOD U.R.F./C.C. SERUM ½ HOUR AFTER ADMINISTRATION
1	None	1,500	1 unit
2	None	1,500	None
3	None	1,500	1 unit
4	None	1,500	Trace
5	None	1,500	½ unit
6	None	3,000	1 unit
7	None	3,000	None
8	None	3,000	¾ unit
9	None	3,000	1½ unit

*Blood specimens drawn before Lutrexin was given.

Clinical Material

In the present study 90 women who complained primarily of painful menstruation have been treated with tablets of U.R.F.* They were all intelligent women, capable of evaluating the results, chiefly nurses, technicians, and aides on the hospital staff. No effort was made at the onset of treatment to differentiate the etiological factors of the dysmenorrhea. All had had some medication during previous periods of dysmenorrhea. None were told the nature of the new drug or what to expect in the way of amelioration of their symptoms except that the drug has been beneficial in tests elsewhere. Tablets were supplied in 500 and 1,000 unit doses. Specific directions were given as to how and when they were to be taken. Only enough calculated for the current period and the ensuing one were given so that the patients would have to return for succeeding doses and to report on the results obtained.

Clinical Results

Of the 90 women in this series 47 had consistently good results with adequate dosage. Fourteen women had partial relief of symptoms, making a total of 61 patients with satisfactory response to therapy. Twenty-nine had no relief; 8 of these women were considered to be inadequately treated and were lost to follow-up examinations when attempts were made to locate them for re-treatment with increased dosage during a subsequent menstruation.

The 47 patients with good results included 24 women who received medication during more than one menstrual cycle. Ten patients were relieved of symptoms by an initial dose of 1,000 units and 1,000 units every 2 to 4 hours. One patient was relieved by an initial dose of 1,500 units, 3 required 2,000, and 29 required 3,000 units with an additional 1,000 units every 2 to 4 hours. One patient required 3,500 units. Seven women were unrelieved by 1,000 or 2,000 units but found 3,000 units were effective.

The group of 14 women who were classified as receiving fair results from medication were sufficiently relieved of symptoms to continue their duties but were still not completely free of discomfort. Two of these women took only 1,000 units at onset of therapy and could not be persuaded to increase their dosage in an effort to obtain additional relief. Four have taken 1,000

*Lutrexin—Hynson, Wescott & Dunning, Inc.

units, two 2,000 units, and two 3,000 units during a single menstrual cycle. Three patients in this group have also had improved results with increased dosage.

Of the 29 women who were considered therapeutic failures, 10 were unavailable for follow-up study. Two of these 10 patients were adequately treated and the remaining 8 are to be considered inadequately treated as they received an initial dose of only 1,000 units with 1,000 units every 2 to 4 hours thereafter. Sixteen of the 19 remaining women who took medication two or more times without relief all received 3,000 units initially or during the second month of therapy. An effort was made to evaluate the pelvic findings and etiological factors contributing to the dysmenorrhea in this group of patients. Nine women were found to have normal pelvic structures, 3 had retroverted uteri and associated menorrhagia. Three had pelvic inflammatory disease, 1 had a myomatous uterus and menorrhagia, 2 had the Stein syndrome, 1 had dwarfism of the achondroplastic type with an infantile uterus, and 2 had severe vaginitis. One had menorrhagia associated with severe hyperthyroidism. However, although the patient is now in a euthyroid state on propylthiouracil medication, she still has excessive bleeding and dysmenorrhea. She obtained some relief if she was able to take her medication before the actual onset of severe cramps. But as she was often awakened from a sound sleep by menstrual cramps, this was frequently impossible. On occasions when it was possible to prevent ovulation with estrogens this patient had no pelvic discomfort. It is of interest that the dysmenorrhea of the achondroplastic dwarf was also relieved by prevention of ovulation. Seven patients refused pelvic examination. Six women in the group were thought to have rather severe anxiety neurosis with associated tension states in addition to other findings.

No side reactions were noted in any of the cases treated. One factor which contributed to the unwillingness to try larger doses was the number of pills to be ingested. In order to overcome this, future use of the drug will employ the tablets of larger unit content. It is also planned to run a concomitant control series by using placebos made up in exactly the same size and configuration. This necessitated the manufacturing of a special pill as the U.R.F. gives the tablet a brown-speckled appearance which is not easily disguised. Like all therapy for dysmenorrhea, U.R.F. seemingly worked better when given early, ideally the day before menses started, and certainly before cramps became severe or nausea occurred.

Summary

A uterine relaxant, a factor obtained from the corpus luteum of sow ovaries, has been isolated and the bio-assay standardized. It has been chemically classified as a protein or polypeptide. This substance is not destroyed in the stomach as the active principle appears in the blood serum within 30 minutes after oral administration in the human being. In a series of 90 women who complained of dysmenorrhea an initial dose of 1,000 to 3,000 units followed by 1,000 units every 2 to 4 hours was sufficient to control the symptoms of 61 women. Twenty-nine women had no results from therapy, but only 21

were considered adequately treated. Although the efficacy of medication for dysmenorrhea is notoriously difficult to evaluate, the fact that a number of women obtained no relief from small doses but adequate relief when larger amounts of U.R.F. were administered leads us to believe that the action is physiological rather than psychological. It seems from this preliminary survey that the uterine relaxing factor is of value in the treatment of dysmenorrhea as it relieves the entire symptom complex and has no sedative effect. It is apparently ineffective in those women with major psychosomatic difficulties or anatomically abnormal pelves. Further studies are planned using larger doses as well as a control series making use of a placebo tablet similar in all respects to those containing U.R.F.

Conclusions

A new drug, capable of acting against dysmenorrhea and to be given orally, has been subjected to limited preliminary clinical tests. It shows enough satisfactory results to warrant its use. Studies will be continued to evaluate it further, especially to determine the optimal dosage.

References

1. Miller, N. F., and Berhman, S. J.: Am. J. Obst. & Gynec. **65**: 505, 1953.
2. Rutherford, Robert N.: West J. Surg. **50**: 598, 1942.
3. Falls, F. H., Rezek, George H., and Bennensohn, S. J.: Surg., Gynec. & Obst. **75**: 289, 1942.
4. Krantz, J. C., Bryant, H. H., and Carr, C. J.: Surg., Gynec. & Obst. **90**: 372, 1950.
5. Felton, Lloyd C., Frieden, Edward H., and Bryant, Harold H.: J. Pharmacol. & Exper. Therap. **107**: 160, 1953.
6. Hisaw, F. L.: Proc. Soc. Exper. Biol. & Med. **23**: 661, 1926.
7. Rezek, George H.: In press.
8. London, Frank: Personal communication.

IS CHORIONEPITHELIOMA DUE TO LACK OF A LYTIC SUBSTANCE IN THE MATERNAL BLOOD?

H. Acosta-Sison, M.D., F.P.C.S., Manila, P. I.

(From the Departments of Obstetrics and Gynecology, University of the Philippines)

THERE has been speculation as to the etiology of the malignant mole or chorionepithelioma. Why is it that the chorionic cells in these conditions multiply inordinately, and even metastasize and continue to grow in any locality they may be transported to?

Several workers, cited by Mathieu,[1] claim that the normal trophoblastic cell of early pregnancy is malignant in the sense that it has an invasive quality by virtue of which the fertilized ovum becomes implanted and nourished through extravasated blood, and that if the trophoblast is prevented from developing into chorionepithelioma, it is due to a protective lytic substance found in the blood of the mother. This lytic substance in the mother's blood automatically dissolves an errant trophoblastic cell that may have wandered by the circulatory route into other parts of the body such as the lungs. It has also been claimed that the teratomatous chorionepithelioma develops because of lack of the lytic substance in the individual.

The presence of this lytic substance among pregnant and parturient women, as postulated by these authors, is the explanation given by most investigators, including Novak,[5] as to why the majority of parturients do not develop chorionepithelioma. Dickson[1] even went to the extent of advocating the intramuscular injection of the blood serum from pregnant or recently delivered women as the rational treatment of chorionepithelioma to provide the necessary lytic substance to dissolve the chorionepithelioma cell.

The lytic theory as expressed seemed plausible and we were about to try the treatment as advised by Dickson when the following cases were seen which seemed to contradict it.

Case 1.—Abortion of twins at 4 months. One was a normal fetus with placenta, the other a hydatidiform mole from which uterine chorionepithelioma subsequently developed.

I. R., 36 years old, gravida vii, para v, was admitted to the Philippine General Hospital on Oct. 22, 1941, with the complaints of vaginal bleeding, uterine pains, weakness, and fatigue for the last twenty days. Her last menstruation was in June, 1941. The day after admission, she aborted spontaneously a 4 months' fetus. The uterus was noted to be still much enlarged after expulsion of the fetus. On manual exploration, it was found to be distended by mole cysts which were evacuated together with the normal placenta of the fetus. The uterus was finally emptied with a big spoon curette. Blood transfusion and venoclysis had to be administered thereafter. The pathological examination of the last curettings was reported by the pathologist to show malignant mole.

Total hysterectomy was performed on Nov. 1, 1941, or 9 days after the dilatation and curettage. The uterus was the size of a 3 months' pregnancy. On sagittal section of the uterus, the endometrium was found to be studded with many red foci of chorionepithelioma ranging from 1 to 2 cm. in size, especially on the posterior wall and below the entrance of the Fallopian tubes. The biopsy showed chorionepithelioma.

CASE 2.—A 2 months' twin pregnancy in which one was a malignant mole and the other a normal fetus with a normal placenta.

F. B., 19 years old, gravida i, was admitted to the Philippine General Hospital on Sept. 25, 1942, with the complaints of vaginal bleeding, weakness, dyspnea, abdominal pain, and sudden abdominal enlargement for the last week. She also complained of fever for the last three days. Her last menstruation was in July, 1942. On admission, she was weak and pale. The fundus uteri was just below the costal arch. The cervix was small and soft.

Blood examination showed: red blood count 2.65 million, white blood count 6,050. The blood pressure was 122/80.

The diagnosis was hydatidiform mole and she was immediately curetted. Many mole cysts were evacuated together with a 2 months' fetus and placenta. Biopsy of the mole was reported as malignant by the pathologist.

Because of lack of blood transfusion and intravenous fluids, the patient succumbed from hemorrhage.

CASE 3.—A 7 months' twin pregnancy. One twin was a living child with a normal placenta; the other was a hydatidiform mole and there was metastatic chorionepithelioma in the vagina, lungs, and brain.

T. A., gravida vii, para vii, entered the Philippine General Hospital on Dec. 9, 1938, with the complaint of vaginal bleeding and labor pains at the eighth month of pregnancy. On pelvic examination, a spongy mass was felt at the partially dilated internal os. Soon after, a mass of hydatidiform mole was expelled, followed by the spontaneous birth of a live 7 months' fetus. The mole preserved its connection with the normal placenta which was expelled spontaneously ten minutes after the birth of the child. Soon after delivery of the placenta, the patient complained of headache, dimness of vision, and dyspnea. These were soon followed by unconsciousness and the twitching of the right arm and right leg. The pulse slowed to 40 to 58 per minute. The blood pressure fell to 40/70. The red blood count was 3.07 million and the hemoglobin 40 per cent. Eye examination showed dilatation of both pupils. The retina and optic disc were pale, otherwise normal. Speculum examination of the vagina showed chorionepithelioma growth on the lower part of the posterior vaginal wall. The patient died soon after losing consciousness.

Autopsy showed chorionepithelioma anatomically and microscopically in the lungs, vagina, and brain with cortical hemorrhages. The fetus weighed 1,500 grams and lived for 5 days.

If the lytic theory of the causation of chorionepithelioma were correct, the coexistence of malignant mole and normal fetus with normal placenta as found in Cases 1 and 2, and the coexistence of mole, metastatic chorionepithelioma, and normal living fetus with normal placenta in Case 3 would not be possible. In the presence of a lytic substance, no malignant mole and much less chorionepithelioma should have developed. And if there were no lytic substance, there should have been no normal placenta with a normal living fetus. Moreover, if it were true that the presence of a lytic substance in the mother's blood is the one that counteracts or neutralizes the invasive quality of the chorionic epithelium, ipso facto, the implantation of the fertilized ovum would not be possible which, of course, is contrary to fact.

In the case of teratomatous chorionepithelioma where the affected individual is supposed not to have the necessary lytic substance and presumably never had it, why is it that the chorionic cell which resided in the individual since fetal existence did not develop chorionepithelioma until some time after puberty?

Is it not more true to fact that the normal trophoblast or chorionic epithelium, unlike the abnormal chorionepithelioma cell, possesses a well-coordinated invasive quality, usually within the confines of the decidua when this is normally developed, as it is in the vast majority of cases, and that the normal invading cells are so well organized with a definite pattern of normal villi with their mesodermic core that their growth takes place only until the completion of the full growth of the placenta? Therefore, if any portion of the villus becomes detached and wanders into any portion of the body it will not thrive because it is not malignant and has lost its connection with its fellow cells. Moreover, in the vast majority of cases, the normal chorionic epithelium after the death or expulsion of the fetus ceases to live and will eventually become absorbed. This is exemplified in cases of ruptured tubal pregnancy or tubal abortion, in missed abortion, and in abdominal pregnancy where the placenta when not removed degenerates in situ.

Greenhill[4] claims that he found a piece of placenta which had remained in a fibromatous uterus for 18 months. And Ries[6] found placental villi in uterine vessels 18 years after the last delivery. These observations show that malignancy in chorionepithelioma resides in the cell itself, not in its environment. When the chorionic cell is not malignant, it degenerates and is cast off, as often happens, or remains in statu quo for some time without proliferation.

This is contrary to the behavior of the chorionepithelioma cell which has the quality of inordinately proliferating itself in localized spots without a definite pattern, breaking blood vessel walls, dissolving tissues wherever it may implant itself. Moreover, it quickly becomes disintegrated.

In cases of placenta accreta where the decidua is poorly developed so that the chorionic villi encroach on the myometrium for their nourishment of the fetus, the chorionic cells are not malignant, they preserve their villous pattern, and take part in the make-up of the placenta. Ordinarily, however, the poorly developed decidua does not encourage the development of the villi and thereby often gives rise to abortion.

In 1950, while I was visiting the Boston Lying-in Hospital, Dr. Hertig showed me the uterus of a patient who had a laparotomy at term because her previous delivery had been by cesarean section. While I do not believe in the dictum, "Once a cesarean, always a cesarean," yet in this particular case it was most fortunate that the laparotomy was performed. On section of the abdominal wall, the peritoneal cavity revealed free blood. The placental villi were found to have penetrated beyond the uterine wall and into the tissues of the broad ligament. Fortunately the operation was performed in time for the baby to be extracted alive. Had it not been for the timely operation, both mother and child would have succumbed from hemorrhage.

The chorionic cells of this patient, though they penetrated beyond the uterine wall, could not be called malignant, not even chorioadenoma destruens, for they preserved their regular villous pattern constituting the organic entity of the placenta for the purpose of nourishing the fetus.

Custo[3] tried to implant placental grafts 3 to 4 mm. square in organs such as the liver, kidney, ovary, and uterus, or in two organs simultaneously, in rabbits and guinea pigs; and 3 to 50 days later sacrificed the animals to find the condition of the grafts. For the heteroplastic grafts in rabbits, woman's placenta was used. In all—the heteroplastic, autoplastic, and homoplastic implantations—the placenta showed marked signs of degeneration and no indication of proliferation or infiltration in any of the organs in which it was implanted. The uterus showed signs of enlargement but the other organs did not show any changes. The animals used were neither pregnant nor recently delivered and therefore presumably had no lytic substance in their blood, yet the chorionic cells, because they were normal (not malignant), not only did not proliferate but degenerated.

The evidence at hand is as follows, namely:

1. The coexistence of (a) malignant mole and normal pregnancy, (b) mole, metastatic chorionepithelioma, and a live baby with a normal placenta as shown in the above reported cases;

2. Greenhill's and Ries' observation in a fibroid uterus of the possible existence of normal nonproliferating and noninvasive chorionic villi in the uterus and uterine vessels from eighteen months to eighteen years after delivery;

3. The automatic degeneration and absorption of the placenta, once the fetus dies or is aborted, as shown in old ruptured tubal pregnancy or tubal abortion, in missed abortion, or in cases of abdominal pregnancy where the placenta is left in situ because of the danger of hemorrhage when it is separated;

4. The failure of the autoplastic, homoplastic, and heteroplastic placental implants to grow and proliferate in any of the different organs of a nonparturient animal (supposed not to have the lytic substance) as demonstrated by Custo's experiments.

This shows that the malignancy in chorionepithelioma resides in the cell itself. The basic cause may be hormonal. It is perhaps the hormone generated by the malignant chorionic cell itself which digests the surrounding tissues and stimulates its proliferation. It is a well-known fact that in hydatidiform mole and chorionepithelioma there is a high titer of the chorionic gonadotropic hormone. This may be the reason for the marked development of the mole cysts and may explain the high percentage of chorionepithelioma growths (over 50 if not 60 per cent) resulting after hydatidiform mole.

The special characteristics of chorionepithelioma with all its subdivisions (choriocarcinoma, chorioadenoma destruens, and syncytioma) are its inordinate purposeless invasiveness toward neighboring tissues which become dissolved at contact, its readiness to break blood vessel walls giving rise to hemorrhages and at the same time facilitating its transportation to other regions, notably the vagina, lungs, and brain, and its lack of definite pattern of villi which constitute the placenta for the specific purpose of nourishing a live fetus. The tendency to metastasis is especially more marked and occurs

in an earlier stage in the choriocarcinoma variety where there is greater preponderance of Langhans' cells. This is not surprising for it is the Langhans' cells that secrete the chorionic gonadotropic hormone.

Summary and Conclusion

Factual evidence is presented to show that the malignancy of chorionepithelioma resides in itself, not in the lack of lytic substance in its environment. The impetus of its invasiveness and proliferation lies perhaps in the excessive chorionic gonadotropic hormone produced by the malignant cell itself. This hormone, in addition to its stimulating action on the cell, has a softening and congestive effect on the surrounding tissues, rendering them more vulnerable to the corroding action of the malignant cell.

References

1. Mathieu, A., and Robertson, T. D.: Internat. Abstr. Surg. 69: 158, 1939.
2. Acosta-Sison, H.: Philippine M. World 1: 1, 1946.
3. Custo, E. L.: Surg., Gynec. & Obst. 69: 157, 1939 (Abstract).
4. Greenhill, J. P.: DeLee-Greenhill Principles and Practice of Obstetrics, ed. 10, Philadelphia, 1951, W. B. Saunders Company, p. 757.
5. Novak, E.: Personal communication.
6. Ries: Quoted by Greenhill.[4]

THE TREATMENT OF CERVICAL EROSION BY A SIMPLE METHOD OF ELECTROCOAGULATION

EDWARD A. GRABER, M.D., AND JAMES J. O'ROURKE, M.D., NEW YORK, N. Y.

THE most common of all gynecological lesions seen both in general practice and in the specialty of obstetrics and gynecology is the cervical erosion. Kleegman[7] has stated that it is the most common pathologic lesion found in the pelvis. In a series reviewed by this author it was reported that 20 per cent of nulliparas and 78 per cent of multiparas were affected with this disease. Polak[13] concluded that 85 per cent of women have some degree of cervical infection.

Any advance in the treatment of such a common condition is worthy of discussion. The purpose of this paper is to report a simple coagulation method of treating erosions of the cervix.

Until 1949, we accepted what appeared to be the consensus in the literature that cauterization of the cervical erosion with the nasal tip cautery was the safest and best method. We were, however, not completely satisfied. Our objections to the nasal tip cautery were, first, that this type of treatment, while available in the specialist's office, was often not found in the office of the general practitioner. Second, the patients' reactions to the hot cautery were not pleasant. Many complained of a feeling of heat and of pain. The charring odor of burned tissue was most distressing, and the odoriferous discharge following slough was repugnant. Third, because the depth of penetration was not easily controlled, incidence of delayed hemorrhage, stenosis of the canal, and the occasional spread of the infection in the parametrium were more frequent than one would ordinarily expect from the so-called safest method of treatment. Finally, the length of time for complete healing after nasal-tip-cautery treatment also seemed to us to be unnecessarily prolonged. It was usually found that the slough detached itself in about three weeks, and this was followed by granulation and cicatrization. However, in most instances, due to conservative cauterization, additional areas of erosion were still seen after a period of four to six weeks, and these had to be recauterized.

Several articles made us change our approach to the treatment of cervical erosion. Findley[4] found that treatment by coagulation produced the most satisfactory results in 240 cases of cervical erosion. His second-best results were after conization, and least impressive were those after cauterization. His findings indicated that the most complications followed conization, chief among which were hemorrhage, stenosis, pyometra, and parametritis. Histologically, there was more fibrosis after cauterization and very little with coagulation alone.

Maryan[9] indicated that with coagulation, more uniform, controlled penetration of heat and minimal carbonization were possible. It gave a more even

slough resulting in less hemorrhaging. Lovelady,[8] at the Mayo Clinic, found that the treatment of cervicitis with electrocoagulation gave excellent results in chronic endocervicitis with erosion. He advocated that it be done in the office without anesthesia. As early as 1929, Ende,[3] using electrocoagulation in 200 patients, found more rapid healing and less scarring than with other methods.

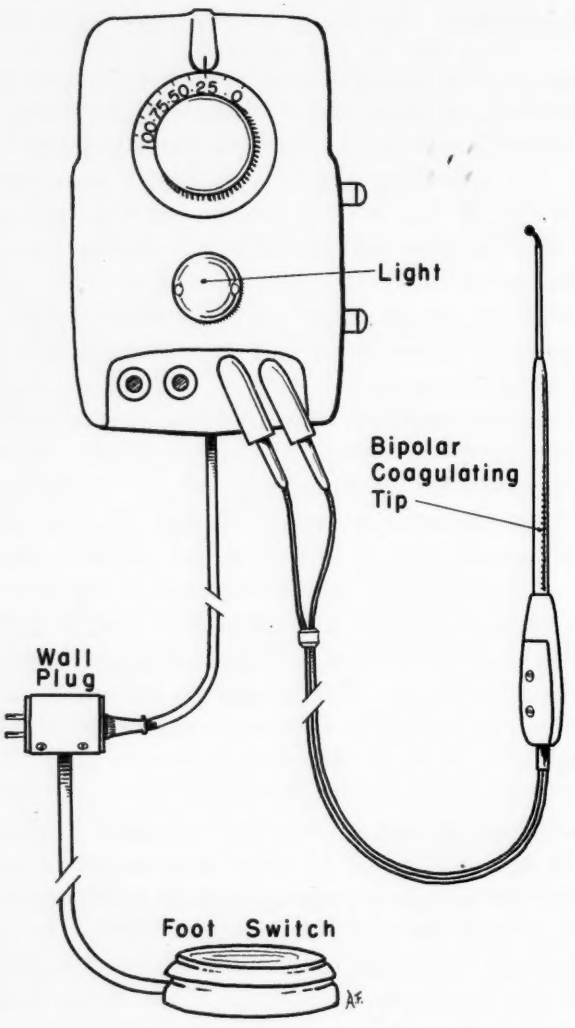


Fig. 1.

Nowhere in the literature could any article be found that condemns the use of electrocoagulation. It therefore seemed logical thoroughly to investigate its effects.

Our next problem was to find a machine that, first, could accomplish the job efficiently and, second, would be cheap and available to most physicians who might be called upon to treat cervical erosions. Investigation of diathermy machines and electrosurgical units commonly available on the market revealed that, generally, they cost hundreds of dollars and probably were be-

yond the means of a physician who treated an occasional erosion. Further search, however, revealed that, if a special coagulator tip could be devised for a small portable spark-gap diathermy apparatus* in common use throughout the country, this unit could be used effectively.

This machine is essentially a small, portable spark-gap diathermy (Fig. 1). Its primary use is apparently for desiccation and fulguration but it has bipolar outlets. The dial on the front of the machine controls the intensity of the current by turning it clockwise from 0 toward 100. By using our specially devised bipolar coagulator, which consists essentially of a metal ball split in the middle, with an insulator between, sufficient heat can be created in the tissues of the cervix actually to destroy the diseased cells. The principle of coagulation is to create a temperature high enough to cause coagulation of the protein in the cells, thus ending their lives. They are then sloughed off by the body, leaving behind a simple wound to heal.

The method described here, even in the hands of a less experienced operator, is a safe and simple one. The flow of current is restricted between the two halves of the ball. Only tissue lying between these halves, therefore, is subject to the action of the heat. Stray currents, or too deep penetration, become almost an impossibility. It is this that makes coagulation of the cervical erosion an office procedure. Undercoagulation rather than overcoagulation is all that the physician need remember in its application.

Mild coagulation of the vaginal aspect of the eroded cervix has been done with success in our series of cases. Further, it was found that cysts could be punctured with a needle-point attachment, which comes as standard equipment, and then could be desiccated, using the unipolar lead on the machine.

Technique

Insert a suitable bivalve speculum. If one is careful not to touch the metal speculum, this can be used in most cases. A Bakelite or plastic speculum is preferred. No anesthesia is required. Any mucous discharge is wiped away with cotton balls. A sufficient current should be employed so that, when the foot switch of the Hyfrecator is pressed, there is penetration of about 2 mm. by the electrical current. It has been our experience that this can best be done by setting the dial at about 75 to 90. The coagulating ball is put against the area of the cervix to be coagulated and then the current is turned on by means of the foot switch. The current is applied until a whitish-gray area appears and then is immediately cut off. Using this technique, the entire vaginal surface of the erosion is coagulated (Figs. 2, 3, and 4).

It is better to use a little less current for a slightly longer period of time than high current for a short time. In this way, one will tend to undercoagulate rather than overcoagulate, and it is much safer to do the former. The canal is not entered. We believe that this is an important factor in the safety and lack of complications of the treatment. In some cases of marked ectropion due to chronic laceration, the area is stripped at 6, 12, 3, and 9 o'clock.

In the follow-up therapy, no sulfonamide creams or antibiotics are used. If a severe endocervicitis exists with a profuse purulent discharge coming from the canal, penicillin parenterally is given in preference to local therapy.

*The type of apparatus used in this work was the Birtcher Hyfrecator manufactured by the Birtcher Corporation, Los Angeles, Calif.

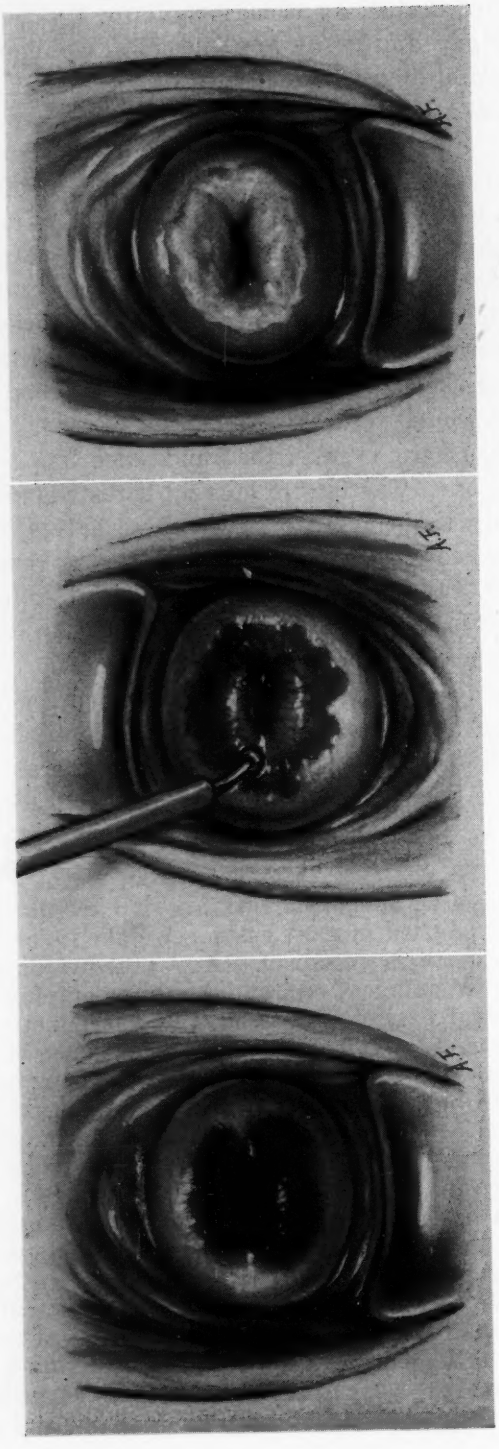


Fig. 4.

Fig. 3.

Fig. 2.

Fig. 2.—Original cervical erosion.
Fig. 3.—Application of coagulating current to erosion.
Fig. 4.—Appearance of cervix after surface is coagulated.

The patient is warned that vaginal spotting may occur about the third to the sixth day after treatment. She is told to abstain from sexual intercourse, douching, and tub baths and urged to report at once if there is excessive bleeding. After one week has passed, if there is no bleeding, it is recommended that she douche daily with a solution of vinegar and water and return two weeks after her original coagulation.

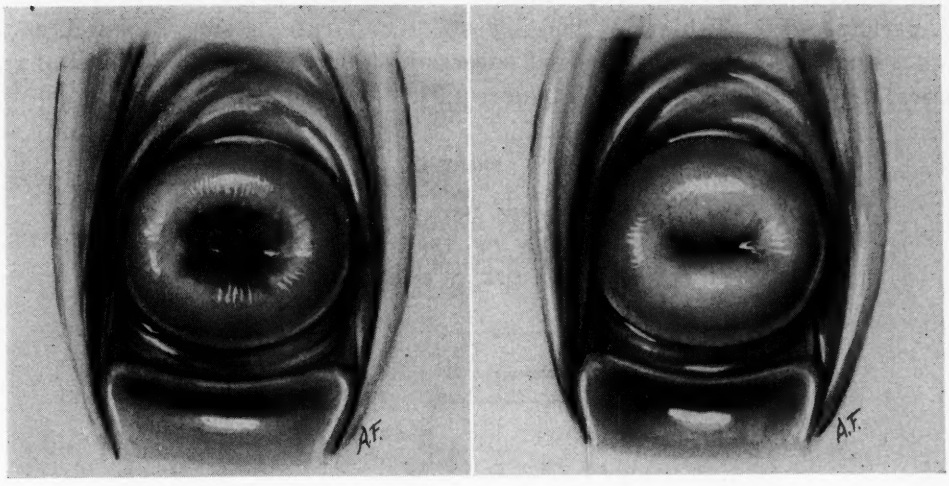


Fig. 5. Fig. 6.

Fig. 5.—Healing erosion with pink new mucosa at periphery.
Fig. 6.—Healed erosion.

Careful daily observation in selected cases has shown that the coagulum sloughs between about the fourth and the sixth days, leaving a clean granulating surface beneath it. When the patient returns two weeks later, one can see light-pink mucous membrane growing in from the periphery and the diameter of erosion is diminished (Fig. 5). The treatment is repeated every two weeks and the same instructions are given for each two-week period until healing is complete (Fig. 6). If possible, patients are not treated near the time of menses, so that there will be no confusion about hemorrhage.

Contraindications

Before discussing the results obtained in our series, the contraindications to the use of coagulation should be emphasized:

1. It should not be used too near the postpartum period, especially if there has been fever during that time.

2. It should not be used during the acute stages of cervicitis. The infection should be brought under control first by antibiotic therapy.

3. It should not be used unless smear or biopsy is taken in any case where there is a question of malignancy.

4. It should not be used during the acute stage of salpingitis, or acute or subacute parametritis.

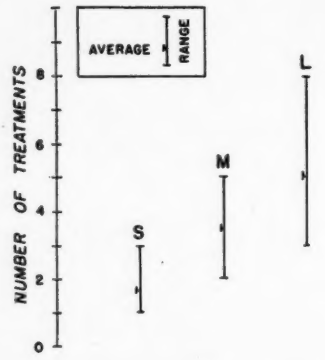
Results

The results in our series and the complications are presented in the accompanying tables and charts. Cases were abstracted in sequence, beginning in July, 1950, until data on 100 cases had been tabulated. The date of treatment of the one hundredth case was April, 1952.

The cases were tabulated first as to result of the sequence of treatments. Only one case was classified as "failure" and in only two of the cases was any hemorrhage seen (Table I). The lowest "true" rate of success which could give a sample result of 99 per cent success in 100 cases at the .05 level of statistical significance is 94 per cent success.

CHART I

RANGE AND AVERAGE
NUMBER OF TREATMENTS
BY SIZE OF EROSION



Analysis of the number of treatments necessary to clear up the erosion indicates that the larger the size the greater the number of treatments required (Table II). Erosions were classified as "small" if the diameter was less than 1.5 cm., "medium" if less than 2.5 cm., and "large" if over 2.5 cm. The differences are statistically significant and could not have occurred by chance more than once in a thousand samples. However, it should be noted that the range of the number of treatments for each classification size overlaps the range of the succeeding size (Chart I).

TABLE I. RESULTS OF TREATMENTS

RESULT	NUMBER OF CASES	HEMORRHAGE	
		YES	NO
Success	99	2	97
Failure	1	0	1
Total	100	2	98

Cross-classification of the cases as to age of patient and size of erosion indicates that there is no statistical significant difference in the age distribution for the three size determinations. Thus, the difference in average number

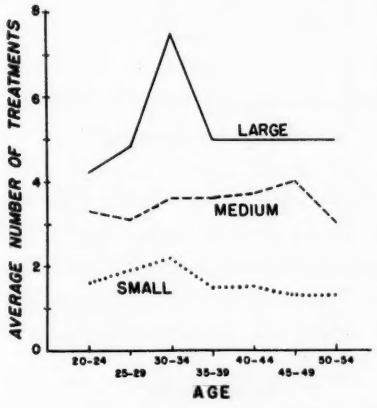
of treatments for each size of erosion (Table II and Chart II) is not due to a difference in the age composition of cases in each group. The average number of treatments for each age group and size, upon statistical analysis, differs only because of the size of the erosion.

TABLE II. AVERAGE NUMBER OF TREATMENTS

SIZE OF EROSION	NUMBER OF CASES	AVERAGE NUMBER OF TREATMENTS
Small	34	1.7
Medium	45	3.5
Large	21	5.0
Total	100	3.2

CHART II

AVERAGE NUMBER OF TREATMENTS
BY PATIENT'S AGE
AND BY SIZE OF EROSION



The degree of laceration has no effect upon the number of treatments within each size classification. As with the age factor, the pattern indicates no correlation with degree of laceration (Chart III).

Follow-up of the cases subsequent to the last treatment has not indicated any recurrence of the erosion.

A short résumé of the "failure" case may be of interest.

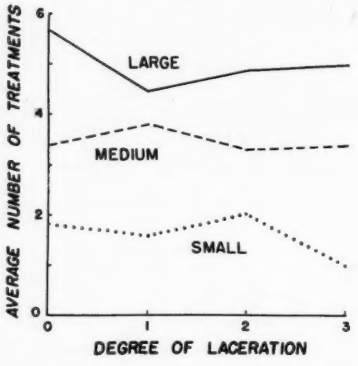
The patient was a 48-year-old nullipara who had a large erosion. The vaginal smear was negative for malignancy. Coagulation therapy was initiated, but after four treatments, no progress was noted. Multiple biopsies were performed to be sure that malignancy was not overlooked, and these were reported as chronic cervicitis. This was followed by two more attempts at coagulation which were disappointing. The patient was given a rest for one month and then the cervix was cauterized by nasal-tip cautery. The result was unsatisfactory after six weeks. Inasmuch as she also had small fibroids, a total hysterectomy was advised. This was done without event and sections of the cervix confirmed the diagnosis of cervicitis.

The two cases of hemorrhage also bear further explanation. In both these cases, what the patient interpreted as hemorrhage occurred after the second

treatment. In one, the patient lived about 40 miles away and her local doctor packed the vagina. This was sufficient to control the bleeding and recovery was uneventful. No blood was replaced. In the second, a vaginal pack also sufficed, and the erosion healed completely a short time later. In neither case was the bleeding excessive.

CHART III

AVERAGE NUMBER OF TREATMENTS
BY DEGREE OF LACERATION
AND SIZE OF EROSION



In conclusion, we wish to emphasize again that coagulation is a safe, effective and simple way to treat erosions of the cervix. We have devised a special electrode to fit a machine that is inexpensive and already in the hands of 90,000 physicians in the United States. Our results were excellent, and we recommend this form of therapy to anyone interested in its use.

References

1. Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, 1933, W. B. Saunders Company, vol. 3, p. 542.
2. Davis, C. H.: Gynecology and Obstetrics, Hagerstown, Md., 1953, W. F. Prior Company, vol. 3, chap. 7.
3. Ende, F. M.: Am. J. Obst. & Gynec. **18:** 72, 1929.
4. Findley, A.: Am. J. Obst. & Gynec. **49:** 614, 1945.
5. Holden, R. C.: Am. J. Obst. & Gynec. **16:** 624, 1928.
6. Hyams, M.: in Meigs, J. V., and Sturgis, S. H., editors: Progress in Gynecology, New York, 1946, Grune & Stratton.
7. Kleegman, S. J.: Am. J. Surg. **68:** 294, 1940.
8. Lovelady, S. B.: S. Clin. North America **27:** 848, 1947.
9. Maryan, H. O.: M. Clin. North America **27:** 99, 1943.
10. Novak, E.: Textbook of Gynecology, ed. 3, Baltimore, 1948, Williams & Wilkins Company, p. 201.
11. Stein, I. S.: S. Clin. North America **30:** 259, 1950.
12. Weiner, A.: Am. J. Obst. & Gynec. **62:** 1106, 1951.
13. Polak, J. O.: Pelvic Inflammation in Women, New York, 1926, D. Appleton & Company, p. 14.

540 Park Avenue

NEONATAL INFANT MORTALITY

Before and After the Use of the Air Lock for the Treatment of Newborn Infants in a Large Maternity Hospital

ALLAN BLOXSOM, M.D., AND SISTER MARY ANGELIQUE, HOUSTON, TEXAS

(From the Department of Pediatrics of the St. Joseph's Children's Hospital and the Baylor University College of Medicine)

IN 1950 and 1951, reports[1, 2] were made on a new method of oxygenation of the newborn infant as a means of treatment during resuscitation, and the statement was published that "The mortality rate in a large maternity hospital has been lowered approximately 25 per cent from a slight reduction in the premature delivery rate and the use of the positive pressure oxygen air lock in resuscitating asphyxiated newborn infants."

Nineteen fifty-two marked the third year the Bloxsom Air Lock has been in use in the St. Joseph's Maternity Hospital in Houston where 6,000 and more deliveries occur each year. Two air locks are in use in the delivery rooms and three air locks are in use in the premature and recovery nurseries. These air locks have been widely used, particularly during the year 1952. Ten per cent of the infants who do not breathe spontaneously are placed in the Bloxsom Air Lock; 50 per cent of the infants are at term and the remainder are premature.

In January, 1953, an adverse critical evaluation[3] of the air lock from New York City appeared, based on attempts to make the air lock function as a barospirator for apneic adult dogs. Such a function, of course, was never intended or claimed for the air lock. It was thought, therefore, at this time it would be interesting to compare the mortality rates of the term infant and the premature infant of 1949, the year before the air lock appeared, and 1952, the year the air lock has been generally used, in an effort to determine if there has been any lowering of the infant mortality when the only change in the treatment of the handicapped newborn infant in the hospital has been the use of the air lock.

Table I shows the neonatal death rates of all infants for the years 1949 and 1952 in the St. Joseph's Maternity Hospital in Houston during the first forty-eight hours of life.

The mortality rate of the term infant delivered in the St. Joseph's Maternity Hospital in Houston during the year 1952, the third year the air lock was in use, fell from 63 per 10,000 term deliveries in 1949 to 37 per 10,000 term deliveries in 1952, a reduction of 41 per cent. This represents a salvaging of 26 term infants in 1952 from a previous loss of 63 term infants

per 10,000 deliveries in 1949. The only difference in handling the term infant between 1949 and 1952 has been a widespread use of the air lock for oxygenation and processing, particularly in difficult resuscitations.

TABLE I. NEONATAL DEATH RATE, FIRST FORTY-EIGHT HOURS OF LIFE, ST. JOSEPH'S MATERNITY HOSPITAL, HOUSTON, TEXAS

YEAR	NO. INFANTS DELIVERED		TERM INFANT DEATHS (2,500 GRAMS AND OVER)	PREMATURE INFANT DEATHS (LESS THAN 2,500 GRAMS)
1949	Prematures	377	37	84
	Term	5,918	(63 per 10,000)	(2,228 per 10,000)
	Total	6,295		
1952	Prematures	452	21	68
	Term	5,702	(37 per 10,000)	(1,504 per 10,000)
	Total	6,154		
Salvage in 1952			26 per 10,000 41 per cent	724 per 10,000 32.5 per cent

Table II shows the neonatal death rates of premature infants in all weight groups for the years 1949 and 1952 in the St. Joseph's Maternity Hospital in Houston during the first forty-eight hours of life.

TABLE II. NEONATAL DEATH RATE OF INFANTS WEIGHING UNDER 2,500 GRAMS, FIRST 48 HOURS OF LIFE

	WEIGHT (GRAMS)							
	450 TO 1,000		1,001 TO 1,500		1,501 TO 2,000		2,001 TO 2,500	
YEAR	LIVING	DEAD	LIVING	DEAD	LIVING	DEAD	LIVING	DEAD
1949	3 (8%)	36 (92%) 10%	19 (46%)	22 (54%) 11%	31 (76%)	10 (24%) 11%	240 (94%)	16 (6%) 68%
1952	3 (9%)	31 (91%) 8%	23 (82%)	5 (18%) 6%	84 (84%)	16 (16%) 22%	274 (96%)	16 (4%) 64%

TOTAL PREMATURE INFANTS			
YEAR	DELIVERED	LIVING	DEAD
1949	377	293 (77.72%)	84 (22.28%)
1952	452	384 (84.96%)	68 (15.04%)
		Decrease in 1952	7.24%
		Percentage decrease	32.5%

The mortality rate of the premature infant delivered in the St. Joseph's Maternity Hospital in Houston during the year 1952, the third year the air lock was in use, fell from 2,228 per 10,000 premature infant deliveries in 1949 to 1,504 per 10,000 premature infant deliveries in 1952, a reduction of 32.5 per cent. This represents a salvage of 724 premature infants out of a former loss of 2,228 premature infants per 10,000 premature infant deliveries. The only difference in handling of the premature infant between 1949 and 1952 has been the widespread use of the air lock for early and continued oxygenation in order to gain time for survival.

Comment

It is believed that some part of the reduction in neonatal mortality of premature infants has been due to a slight decrease in incidence of the very

small premature infant with a slight increase in the incidence of the premature infant weighing 1,501 to 2,500 grams. However, in the premature infant that weighs from 1,501 to 2,000 grams, the neonatal mortality dropped from 24 to 16 per cent, a drop of 33⅓ per cent. In the premature infant weighing from 2,001 to 2,500 grams, the neonatal mortality dropped from 6 to 4 per cent, a drop of 33⅓ per cent. The reduction in mortality in the neonatal period of the premature infant delivered in the St. Joseph's Maternity Hospital in Houston in 1952 when the air lock was used extensively has been accomplished by the use of the air lock chiefly, and not essentially through an increase in the incidence of larger premature infants being delivered in 1952.

Apparently two mechanisms operate when the air lock is used for processing the handicapped newborn infant. The first mechanism is early and rapid oxygenation. A chart of the rate of oxygenation of an anoxic infant is shown in Table III.

TABLE III. OXYGEN SATURATION READINGS OBTAINED BY AN INFANT OXIMETER ON INITIATION OF RESPIRATIONS BY AN APNEIC INFANT BEING OXYGENATED IN THE AIR LOCK

Mother—Eclampsia.—	*Total Sedation Over 36 Hours.—*		
Morphine sulfate	2 grains		
Meperidine hydrochloride	200 mg.		
Paraldehyde	30 c.c.		
Phenobarbital sodium	25 grains		
Minutes After Delivery.—	*Oximeter Readings in Percentage of Oxygen Saturation.—*		
3 (Adjustment oximeter)	15		
5 (In air lock with cycling)	50		
6 (Infant made initial gasp)	50		
7	65		
9 (Irregular respirations started)			
	Pressures in Air Lock.—		
	3.5 LB.	3 LB.	1 LB.
9	77	83	
10	75	86	
14	83	94	96
16	86	95	95
20	87	97	104

The second mechanism is believed at the present time to be an increased rate of metamorphosis of the low cuboidal cells lining the alveolar sacs brought about by pressure changes in the air lock, whereby these cells change to a flattened type providing a greater surface for the exchange of oxygen and carbon dioxide.[4] Such an increased rate of metamorphosis also may prevent leakage by the pulmonary capillaries into the alveolar sacs, and at the same time provide a means of maintaining the pulmonary pressure.

Summary

1. The reduction in the forty-eight hour neonatal death rate in 1952 in the St. Joseph's Maternity Hospital has exceeded considerably the original optimistic report.

2. There has occurred a reduction in the forty-eight hour neonatal death rate of the term infant in the St. Joseph's Maternity Hospital in Houston from

63 per 10,000 term deliveries in 1949 to 37 per 10,000 term deliveries in 1952 because of early and rapid oxygenation to establish respirations. This is a reduction of 41 per cent and represents a salvage of 26 infants from a former loss of 63 term infants.

3. There has occurred a reduction in the forty-eight hour neonatal death rate of the premature infant in the St. Joseph's Maternity Hospital in Houston from 2,228 deaths per 10,000 premature deliveries in 1949 to 1,504 deaths per 10,000 premature deliveries in 1952, a reduction of 32.5 per cent. This represents a salvaging of 724 premature infants from a former loss of 2,228 premature infants per 10,000 premature infant deliveries.

4. The primary causes for this reduction are believed at the present time to be (1) the rapid oxygenation of the anoxic infant by the air lock and (2) an increased rate of metamorphosis of the low cuboidal cells lining the alveolar sacs brought about by pressure changes in the air lock whereby these cells change to a flattened type causing an increased efficiency of the lungs through providing a greater surface of the cells lining the alveolar sacs for the exchange of oxygen and carbon dioxide.

References

1. Bloxsom, A.: J. Pediat. **37**: 311, 1950.
2. Bloxsom, A.: J. A. M. A. **146**: 1120, 1951.
3. Apgar, V., and Kreiselman, J.: AM. J. OBST. & GYNEC. **65**: 45, 1953.
4. Bloxsom, A.: AM. J. OBST. & GYNEC. **66**: 1172, 1953.

SURVEY OF OPINIONS OF OBSTETRICIANS CONCERNING OFFICIAL REPORTING OF FETAL MORTALITY

EDITH L. POTTER, M.D.,* CHICAGO, ILL., AND SAM SHAPIRO, B.S.,**
WASHINGTON, D. C.

THIS report presents the results of a survey of obstetricians conducted in 1952 to obtain opinions on a number of subjects related to the reporting of live births and fetal deaths (stillbirths). The survey was carried out for a subcommittee of the United States National Committee on Vital and Health Statistics,† which is investigating methods for improving statistics on fetal loss, obtainable through birth and fetal death certificates.

Vital records have for many years been an invaluable source of information on the rates of survival of infants and on causes of death of those who do not survive. In recent years, attention has been directed toward a need for the increased utilization of these records for learning more about fetal mortality during both early and late pregnancy. Present indications are that the total fetal loss in the United States represents a problem of equal or greater magnitude than that of infant mortality at the turn of the century.

As in the case of infant mortality, the vital record has a critical position in helping to cope with the fetal-loss problem. Long-range programs require data concerning the pathologic conditions responsible for this loss, its extent and distribution among various population groups, and the associated medical and social factors. However, an adequate body of reliable and uniformly defined statistics for this purpose has been absent.

In May, 1950, the World Health Organization[1] took a major step to meet this situation by defining for world-wide use the terms "live birth" and "fetal death," and recommending certain procedures for the registration and tabulation of these events. Following this action Yerushalmy and Bierman,[2] under the sponsorship of the United States National Committee on Vital and

*Department of Obstetrics and Gynecology, University of Chicago.

**National Office of Vital Statistics, United States Public Health Service, Department of Health, Education, and Welfare.

†The National Committee was formed by the Surgeon General of the Public Health Service at the request of the Department of State in accordance with the recommendations of the First World Health Assembly. Dr. Lowell J. Reed of the Johns Hopkins University is chairman. The major objectives of the Committee are to promote and secure technical developments in the field of vital and health statistics, and to obtain clearance of national and international viewpoints on vital and health statistics problems.

Members of the Subcommittee (on Causes of Fetal Death) when the survey was conducted were Dr. J. Yerushalmy, Chairman (Professor of Biostatistics, University of California); Dr. George W. Anderson (Assistant Professor, Department of Obstetrics, Johns Hopkins Medical School); Dr. Alan F. Guttmacher (Director, Departments of Obstetrics and Gynecology, Mt. Sinai Hospital, New York City); Mr. William M. Haenszel (Director, Bureau of Vital Statistics, Connecticut Department of Health); Dr. Edith L. Potter (Associate Professor of Pathology, Department of Obstetrics and Gynecology, University of Chicago); Dr. Robert B. Reed (Harvard University School of Public Health); Dr. Edward R. Schlesinger (Director, Bureau of Maternal and Child Health, New York State Department of Health); Dr. Iwao M. Moriyama, ex officio, National Committee on Vital and Health Statistics (Chief, Mortality Analysis Branch, National Office of Vital Statistics); Mr. Sam Shapiro, Secretary (Chief, Natality Analysis Branch, National Office of Vital Statistics).

Health Statistics, reviewed many statements, reports, and studies concerned with fetal mortality statistics in an effort to synthesize current knowledge and opinions on the subject. The results were presented as a starting point for activities to overcome present shortcomings.

A Subcommittee on Causes of Fetal Death was established in 1951 to study some of the findings in order to make recommendations for improving certain phases of the situation. Under consideration were ways to improve the reporting on the vital record of causes of fetal death, and maternal conditions related to the unfavorable outcome. Also considered were such allied issues as the possibility of standardizing criteria used by physicians for determining whether certain births and fetal deaths are reportable and for defining such terms as "abortion."

Conduct of the Survey

The survey here being reported was carried out in an attempt to get information on practices now in use and opinions as to whether certain changes would be of value. Questionnaires were sent in May, 1952, to the chiefs of obstetrical and gynecological services (a) in 103 hospitals that are the major teaching units of 68 medical schools and (b) in a sample of other hospitals (70) accredited for obstetric and gynecologic residency. The sample consisted of every fourth hospital listed geographically in the Sept. 29, 1951, issue of the *Journal of the American Medical Association* (pages 420-424), not already covered because of medical-school affiliation.

Completed questionnaires were received from chiefs of service in 61 of the hospitals* associated with the medical schools surveyed, and from department heads in 52 of the other hospitals. Replies came from physicians located in 32 States (and the District of Columbia), with about the same response rate for each region of the country.

Although the 113 responses reflect conditions in only a small fraction of the several thousand hospitals in the country, about one-twelfth of the hospital births that occurred in the United States during 1951 took place in these institutions. Furthermore, and more important, the influence of this group on obstetric practice extends far beyond the 113 hospitals represented.

The responses indicate that considerable thought was given to each question and that frequently the opinions expressed were arrived at in conference with other members of the department. The items taken up appear to have been of active concern to the obstetricians and the survey was viewed by many with much interest and hope for improvement in the current reporting situation.

Analysis showed that there were no major differences in the information provided by the chiefs of service associated with medical schools and by those in the sample of other hospitals. Accordingly, no distinction is made between these two groups in the following section.

*In a number of cases, letters were received from 2 or more hospitals associated with one medical school. Fifty-three of the medical schools covered by the survey are represented by the 61 hospitals responding.

Background of Questions,* Summary of Findings, and Conclusions

A. Form for Reporting Conditions of Pregnancy and Labor.—

Background.—Birth and fetal death (stillbirth) certificates in most states have asked for information on "complications of pregnancy and labor" and "operations for delivery" for more than 10 years. These items were added to the records primarily to obtain statistics needed by the medical profession and public health agencies in dealing with problems of pregnancy loss and with morbid conditions present in the mother and child at birth.† However, gross underreporting and lack of uniformity in the data appearing on the certificates have appreciably reduced the utility of this source.

Methods for improving the situation are now being studied in several places. A proposal[4] (made and put into use by the New York State Health Department) which appears particularly promising is to replace the present form of the items with lists of conditions that could be checked by the person making the entries. The problem has been to select terms for such checklists, which all physicians would interpret in the same way and which would elicit useful information on illness or abnormal condition (not necessarily of a major character), present in the mother during pregnancy or delivery.

The following checklist, which is on the New York State certificate of birth, was used as the point of reference in the survey for obtaining opinions on the suitability of using such a method for obtaining information.

COMPLICATIONS OF PREGNANCY AND LABOR *(Check at least one item in each column)*

RELATED TO PREGNANCY	NOT RELATED TO PREGNANCY	LABOR	OPERATIVE PROCEDURES
0 ☐ None	0 ☐ None	0 ☐ None	0 ☐ None
1 ☐ Pre-eclampsia	1 ☐ Heart Disease	1 ☐ Placenta previa	1 ☐ Low forceps
2 ☐ Eclampsia	2 ☐ Diabetes	2 ☐ Premature separation of placenta	2 ☐ Midforceps
3 ☐ Hypertensive disease	3 ☐ Syphilis	3 ☐ Prolapse of cord	3 ☐ High forceps
4 ☐ Nephritis	4 ☐ Tuberculosis	4 ☐ Anomaly of cord	5 ☐ Cesarean section
5 ☐ Pernicious vomiting	x ☐ Other—specify	5 ☐ Breech presentation	6 ☐ Breech extraction
6 ☐ Pyelitis		6 ☐ Other malpresentations	7 ☐ Internal version and extraction
7 ☐ Anemia		7 ☐ Contracted pelvis	x ☐ Other—specify
x ☐ Other—specify		8 ☐ Other dystocia	
		9 ☐ Postpartum hemorrhage	
		x ☐ Other—specify	

Was mother's blood tested for Rh factor?
No ☐ Yes, Rh + ☐ Yes, Rh - ☐

Survey Findings.—The New York State checklist form for grouping "complications" appeared satisfactory in its main details to 105 of the 113 physicians answering the questionnaire. Most of the other 8 proposed revisions in the titles and arrangement of the checklists, while one felt that the information should not be collected on the vital record.

A large majority of the physicians (79) suggested changes in one or more of the terms included in the checklists. In all, about 220 specific recommenda-

*See Appendix I for wording of questions.

†For an example of an analysis of the data see "Report of Study of Complications Shown on Birth Certificate Supplement," by Mr. William M. Haenszel,[3] Director of the Bureau of Vital Statistics, Connecticut Department of Health.

tions were made, with 4 out of 5 calling for the addition of new items. The others were divided among suggestions for moving an item from one list to another, revising the wording, and dropping items. The new terms that were mentioned reflected a broad range of interests and ideas but only each of the following was advised by more than 10 physicians: "viral infection," "analgesia and anesthesia," "uterine inertia or prolonged labor," "induction of labor," "type of cesarean." The largest number of suggestions for changes in wording (12) concerned the item on the Rh factor.

Less than half the hospitals (45) are interpreting "complications" as referring to both serious and minor disturbances in the mother during pregnancy and labor. In 40 hospitals, only serious conditions are classified as "complications," and in the balance there is generally no uniform interpretation of the term.

Conclusion.—A checklist form (i.e., a modification of the New York State version) for reporting "complications" would probably be acceptable to the great majority of obstetricians. It is apparent, however, that the form would have to be supplemented by an agreed-upon definition of "complications," which would be used by the profession.

B. Medical Entries on Birth and Fetal Death Records.—

Background.—There has been virtually no authoritative information concerning who enters the medical data on the birth and fetal death record. The general impression that has gained ground in recent years is that the attending physician only rarely makes such entries, the function being discharged by other hospital personnel. The validity of this assumption is of considerable significance in designing programs for the improvement in reporting medical data. It is important under all circumstances that the physician realize his responsibility for such information, regardless of who actually makes the entries.

Survey Findings.—The attending physician assumes sole responsibility for entering medical or health information on the live birth record, in almost half the hospitals (51 of the 113 hospitals with which the responding obstetricians are associated). He carries out this function more frequently in connection with the fetal death record (70 hospitals).

In about 30 of the institutions, various hospital staff members, including the resident physician, the medical record librarian, and the nurse also perform this task. In the remaining hospitals, where the attending physician does not make the entries at any time, it is principally the medical record librarian who is given this responsibility (i.e., 17 hospitals in the case of the live birth record and 8 for the fetal death record). Other staff members called upon in some of these institutions include the residents, nurses, and aides.

Conclusion.—In any effort to improve quality of medical data on the birth and fetal death records, it is necessary to reach primarily the attending physician. This type of program would also have to be directed via the hospital administrator toward a variety of groups on his staff.

C. Practices in Reporting Live Births and Fetal Deaths.—

Background.—For a number of years, the national definition has specified that a product of conception showing evidence of "heart action" or "breathing" or "movement of voluntary muscle at birth" is to be considered a "live birth." This is irrespective of pregnancy duration or physical measurement of fetal development.* Most state regulations for reporting live births are designed to conform with this definition, although in some instances they lack the specificity of the national definition.

Until recent years, there was little concern with the precision or uniformity of criteria for reporting live births. The effect of slight variations in applying standards to early fetuses was considered a detail of little significance in deriving most rates in which there was an interest; e.g., total infant mortality rates. However, now that attention is directed toward measuring the survival of very prematurely born infants and to the extent of fetal loss, the use of uniform standards for reporting "live births" is of considerable importance. The survey inquired about actual reporting practice in an attempt to find out how this agreed with the regulations.

In the case of "fetal deaths," it has been well known that variations exist among the state statutes (and regulations) in the criteria concerning minimum period of gestation and evidence of life for reporting these events. However, it was not clear whether there were any differences among physicians in the interpretation of the regulations.

Survey Findings.—There is considerable variation among the hospitals covered in criteria for registering live births. Less than half (45) report all births in which any "evidence of life" is indicated. Sixty-four use gestation age or physical measurement standards to determine whether the birth should be registered and, in four hospitals, other factors are introduced. There is a fairly widespread belief that "fetal death" and "live birth" reporting start at the same point. In some hospitals, however, the emphasis is on whether the fetus is "viable" and various measures are used to make this judgment.

Distribution of the 64 hospitals according to measurement criteria used for reporting "live births" follows:

NO. OF HOSPITALS	STANDARDS FOR REPORTING BIRTHS
5	Weight alone (ranging from 400 to 1,500 grams)
5	Fetal length alone (25 cm.)
29	Gestation age alone (ranging from 12 weeks to 5 months)
16	Combination of two of the measurements—weight, gestation age, fetal length (ranging from 18 weeks/750 grams to 28 weeks/1,000 grams)
9	Combination of all three measurements (ranging from 22 weeks/500 grams/20 cm. to 28 weeks/1,000 grams/35 cm.)

Many of the obstetricians (52) gave their state regulations as the basis for reporting fetal deaths.† In the remaining cases other factors were

*See Appendix II for wording of definitions of live birth and fetal death in effect during the 1940's and in the past 2 to 3 years.

†At the time the survey was conducted, all but a few of the states required the reporting of fetal deaths that occurred at or after reaching the twentieth week (or fifth month) of gestation. No other measurement criteria were specified, except in one state.

mentioned in what appears to be principally an effort to approximate the requirement through use of another measure (e.g., fetal length for gestational age). The result is a great deal of variability in reporting standards because of the different concepts among physicians as to what criteria are equivalent and which are the most accurate. This explains, to a marked degree, the differences noted above for "live births."

Conclusion.—Variation in criteria for registering "live births" appears to come, in part, from the tendency to have them parallel the standards used in reporting "fetal deaths." Clarification of present regulations would probably help overcome this. However, in view of their specificity and all-inclusive character, use of the internationally recommended definitions of live births and fetal deaths would appear to be the best means of obtaining uniform reporting of both events.

The survey also indicates that a discussion of the reasons for not limiting live births to a certain period of gestation would be an important feature of any program to improve the current situation. Discarding the term "viability," which is subject to many interpretations as a limiting factor in reporting live births, is particularly appropriate at this time since increased attention is being given to the survival of infants born earlier and earlier in the gestation cycle.

D. Definition of "Abortion".—

Background.—Many definitions have appeared in the literature for the term "abortion." These have overlapped definitions of live birth and fetal death, and have caused confusion as to what the latter terms actually meant.

To end this confusion, the World Health Organization[1] recommended that "the term 'abortion' as applied to products of conception should be retained only if essential for internal use within a nation." No attempt was made by the World Health Organization to define "abortion."

To obtain opinion on the matter within the United States, the survey asked whether the physicians considered it essential to retain the term "abortion" for describing certain products of conception in statistical analyses; and if so, how it should be defined.

Survey Findings.—There is strong sentiment for retaining the term "abortion" (82 answered yes to the above question). Amplifying statements from the physicians suggested that at least half were apparently referring to the "delivery" rather than to the "fetus." Such phrases as "expulsion of fetal products," "pregnancy termination," "induced and therapeutic abortions" appeared in their answers.

Two important attitudes are apparent: (a) the definition should cover the pregnancy cycle prior to the point at which registration of vital events begins and (b) the definition should attempt to distinguish between "viable" and "previable" fetuses (some of the physicians mentioned the definition in the Standard Nomenclature as a basis for making this distinction).

Conclusion.—The term "abortion" seems to be deeply entrenched in the language of the obstetrician and the survey suggests it would be desirable to

seek a clear and satisfactory definition rather than attempt to drop the term. In this effort, however, it would be necessary to find a way to avoid confusion with the definition and reporting of live births and fetal deaths.

E. Reporting Cause of Fetal Death on the Certificate.—

Background.—The medical certification section on the fetal death (stillbirth) certificate now in effect in practically all states is in the form of a two-part question: one part requesting information on the "fetal cause," the other on the "maternal cause." Considerable dissatisfaction has resulted from this situation. Frequently it is uncertain, when entries appear in both parts, which condition the physician himself considered to be the underlying cause. Arbitrary rules for coding the information have therefore been developed.

Another problem in attempting to utilize the fetal death record for studying causal factors has been the high proportion of ill-defined causes given on the record (or no causes at all).

It has been suggested that opportunity for improvement would be enhanced if the medical certification on the fetal death record conformed with the corresponding section on the present certificate of death. The physician indicates on this form the immediate and antecedent causes of death. The underlying cause is determined from the sequence of causal factors leading to the death, as given by the physician.

The obstetricians surveyed were asked for their choice between the present form on the fetal death record and the sequential arrangement described. They were also requested to suggest any other measures that might help improve reporting information concerning the cause of death.

Survey Findings.—A sequential arrangement of causes of fetal death is highly favored. Ninety-one of the obstetricians felt that this approach would provide a better basis than the current form for interpreting the cause (or causes) of fetal death.

Many of the physicians (68) also offered suggestions for other measures to improve reporting of the data. The most frequently mentioned were the development and circulation of a list of acceptable terms (20), performance of autopsies (17), and stimulation of professional interest in fetal mortality (9).

Several of these physicians, while believing some advances could be made, had reservations concerning the degree to which the problem of reporting a cause of fetal death can now be solved. There was an additional group of about 10 who felt that practically no improvement could be expected, since in their opinion the cause of fetal death frequently is undetermined even after autopsy.

Conclusion.—Introduction of a sequential arrangement of causes of fetal death on the vital record is considered an important step in obtaining improved reporting of this information. The change, however, needs to be linked with a long-range program that makes known to the obstetrician standards in terminology and in procedures for certifying causes of fetal death. Although greater attention is now being paid to the subject than in

any previous period, the interest of the medical profession in fetal mortality requires further stimulation. The suggestion that more autopsies be performed would then have a greater prospect for adoption.

Summary

The data obtained from the survey clarify current practices and make available many valuable suggestions. They show more precisely than was previously known the wide variation that exists among obstetricians in their interpretation and approach to many of the questions being studied.

It is apparent that a significant reduction of such differences and improvement in reporting medical information will require a multiple-stage activity which would make the appropriate groups aware of the problems; and would lead to joint consideration of the issues by responsible authoritative bodies in the medical profession, registration and statistical fields, with a resultant agreement on definitions and standards. The survey provides information needed to proceed in this direction.

References

1. World Health Organization: International Recommendations on Definitions of Live Birth and Fetal Death, Public Health Service Publication No. 39, National Office of Vital Statistics, Washington 25, D. C.
2. Yerushalmy, J., and Bierman, Jessie M.: Obst. & Gynec. Surv. 7: 1, 1952.
3. Haenszel, William M.: Connecticut M. J. 15: 148, 1951.
4. Lilienfeld, A. M., Parkhurst, E., Patton, R., and Schlesinger, E. R.: Pub. Health Rep. 66: 191, 1951.

Appendix I

QUESTIONS AND RESPONSE CATEGORIES IN THE SURVEY

1. Do you believe that the four major groups on the New York State form, namely, "Related to Pregnancy," "Not Related to Pregnancy," "Labor," and "Operative Procedures," represent a satisfactory way to group the "complications"?

   ☐ YES ☐ NO—a more satisfactory set of categories would be: (explain)

2. What changes if any would you suggest in the items included under each of the four checklists on the enclosed form? (It would be most helpful if suggested changes were accompanied by brief statements giving the reasons.)

   (Response categories "No change," "Would add," and "Would delete" provided for each of the checklists mentioned in Question 1.)

3. Are there any other special items of information relating to the course of the pregnancy and delivery which you think important enough to add to the birth and/or fetal death (stillbirth) certificate?

   ☐ NO ☐ YES (explain) ----------

4. To the best of your knowledge, how is the term "complications" being interpreted by most physicians in your hospital? (Check one)

   ☐ No uniform interpretation.
   ☐ Only illnesses or defects seriously affecting the successful termination of pregnancy.
   ☐ Any serious or minor illness or defect present in the mother during pregnancy or labor.
   ☐ Other (specify) ----------

5. In your hospital, who enters medical or health information . . .

   (a) *On the birth certificate?* (check more than one, if necessary)
   ☐ Attending physician ☐ Medical record librarian ☐ Nurse ☐ Other (specify)

   (b) *On the fetal death (stillbirth) certificate?* (check more than one, if necessary)
   ☐ Attending physician ☐ Medical record librarian ☐ Nurse ☐ Other (specify)

6. Is it the practice in your hospital to report as live births *all* fetuses meeting the above criteria* (including fetuses of 12 to 14 weeks' gestation or less, delivered by abdominal hysterotomy because of maternal complications)?

   ☐ YES ☐ NO Comment:

7. If the answer is "no," what criteria are used to determine whether or not any given conceptus "born alive" according to the above standards is to be reported? (Check one)

   ☐ Weight alone—Specify
   ☐ Fetal length alone—Specify
   ☐ Gestational age alone—Specify
   ☐ Combination of factors—Specify

8. At the present time, what criteria does your hospital use for determining whether the expulsion of a dead fetus is to be reported on a certificate of fetal death (stillbirth)? (Answer in terms of criteria given in Question 7).

9. Do you believe it essential to use the word "abortion" as a descriptive term in statistical analyses for certain products of conception?
   ☐ YES ☐ NO If "Yes," how should it be defined?

10. Which do you believe would provide a better basis for interpreting the cause (or causes) of fetal death, the present form or a sequential arrangement as on the death certificate? (Check one)

    ☐ Present form ☐ Sequential arrangement ☐ No difference

    Comment:

11. A high proportion of the fetal death records give ill-defined causes of fetal death (or no causes at all). What measures, besides a possible change in the medical certification section, do you believe would help overcome this problem? (If you do *not* think the situation can be improved, please give your reasons.)

Appendix II

Definitions of Live Birth and Fetal Death (Stillbirth)

Definitions Appearing in Physicians' Handbook—1949 Edition (issued by the National Office of Vital Statistics, Public Health Service, Department of Health, Education, and Welfare)

Live Birth—A child showing any evidence of life (action of heart, breathing, or movement of voluntary muscle) after complete birth should be registered as a live birth. Birth is considered complete when the child is altogether (head, trunk, and limbs) outside the body of the mother, even if the cord is uncut and the placenta still attached.

Stillbirth—A fetus showing no evidence of life after complete birth (no action of heart, breathing, or movement of voluntary muscle), if the twentieth week of gestation has been reached, should be registered as a stillbirth.

*I.e., "heart action, breathing, or movement of voluntary muscle" at birth irrespective of pregnancy duration or physical measurement of fetal development.

Definitions Recommended in May, 1950, by the World Health Organization and Adopted by the National Office of Vital Statistics shortly thereafter (Supersedes the above)

Live Birth—Live birth is the complete expulsion or extracting from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born.

Fetal Death—Fetal death is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation, the fetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles.

In the past 2 years a number of national organizations have endorsed the WHO definitions. These include the American Academy of Pediatrics, the American Committee on Maternal Welfare, the American Medical Association, the American Public Health Association, the Association of State and Territorial Health Officers, and the Public Health Conference on Records and Statistics. Consideration is being given in the state health departments to the possibility of adopting the definitions.

A SIMPLE METHOD FOR THE RELIEF OF POSTPARTUM PERINEAL PAIN

CHARLES BIRNBERG, M.D., AND HOWARD HORNER, M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics, Jewish Hospital of Brooklyn)

PAINFUL perineum is one of the most frequent complaints in the immediate postpartum period of patients on whom an episiotomy has been done to facilitate delivery. Although this condition is of no major consequence as far as prognosis for eventual recovery is concerned, it still represents a factor of considerable concern and discomfort to some patients, even to the point of confining them to bed. On examination of the perineum there rarely can be found any cause for the pain, such as infection or separation of the episiotomy edges. Most of the time there is some induration, and some degree of edema, which are the normal sequel to the healing process of any tissue when absorbable suture material has been used for its repair. Many medications and remedies have been tried in an effort to afford some relief for this condition. These have ranged from simple procedures, such as the application of ice bags, hot water bottles, heat lamps, and anesthetic ointments, to the oral or parenteral administration of sedatives, analgesics, and narcotics.

The purpose of this investigation was to study the effectiveness of Tronothane Hydrochloride (Abbott Laboratories), a water-soluble surface anesthetic ointment to relieve postpartum perineal pain. Tronothane Hydrochloride is a 1 per cent concentration of gamma-morpholinopropyl 4-n-butoxyphenyl ether hydrochloride in sterile jelly. It has a pH of about 5.3 at a 1 per cent concentration, and is comparatively stable.

Two hundred sixty-eight patients were admitted to the Ward Service of the Obstetrical Department of the Jewish Hospital of Brooklyn between Aug. 8 and Nov. 11, 1952. Prophylactic mediolateral episiotomy was performed during the delivery of 252 (94 per cent) patients. Sixty-two, or 24.6 per cent, complained at some time during the first five days after delivery of "painful stitches" to such a degree as to require some medication for relief. In this study no attempt was made to separate the primiparas from the multiparas. All 62 patients who complained of pain were given Tronothane with the instruction to apply the ointment locally to the perineum using a sterile tongue depressor. This was done either by the patient herself or a nurse. In 50 of these patients white petrolatum was substituted temporarily for the anesthetic ointment without the patient's knowledge. The efficacy of the application was measured by the reports of the patients.

Results

With the use of Tronothane some beneficial result was obtained in all patients. Thirty (48.4 per cent) of the 62 patients in this study remarked that the ointment was highly effective in alleviating their discomfort. Thirty

(48.4 per cent) noted moderate effectiveness of the medication and two (3.2 per cent) were only slightly benefited. With the use of petrolatum in a similar tube in 50 of the 62 patients, 26 (52.0 per cent) obtained no relief whatever, and 23 (46.0 per cent) noted some slight improvement. One patient stated that both ointments were highly effective in producing relief of her pain. Thus all of the patients treated with Tronothane reported some measure of relief ranging from slight to marked, while only 23 (46.0 per cent) of the patients who used petrolatum reported slight improvement in their perineal pain, and 26 (52.0 per cent) were not benefited at all (Table I). The slight relief of pain which was reported with the use of petrolatum was in no way comparable to the improvement which occurred with the use of Tronothane. No toxic, allergic, or other untoward effects were encountered in any of the patients treated with Tronothane. Its action was prompt and in most cases effective in reducing the perineal discomfort, thus encouraging early ambulation. No instance of cross sensitivity to Tronothane was encountered in patients who were reported to be sensitive to other topical anesthetic ointments.

Reviewing all the data, and even allowing for some psychological factors as evidenced by the slight relief obtained by some patients who used petrolatum, it appeared that this easily applied and apparently nontoxic medication afforded considerable relief of perineal pain to 96.8 per cent of the patients studied in this series. Although this is only a small series of cases, the results were so gratifying that we are reporting this study in the hope that other obstetricians will observe its effects.

TABLE I. RELIEF OF EPISIOTOMY PAIN BY TRONOTHANE HYDROCHLORIDE

DEGREE OF PAIN RELIEF	NUMBER OF PATIENTS TREATED	
	TRONOTHANE 62	PETROLATUM 50
Highly effective	30 (48.4%)	1 (2.0%)
Moderately effective	30 (48.4%)	None
Slightly effective	2 (3.2%)	23 (46.0%)
No effect	None	26 (52.0%)

Summary

Sixty-two patients were studied to test the efficacy of Tronothane in relieving perineal discomfort in the immediate postpartum period. In 96.8 per cent of the cases, slight to pronounced relief was obtained. In 46.0 per cent of 50 patients in this series only slight relief was reported with the use of petrolatum.

Department of Case Reports New Instruments, Etc.

PITOCIN INDUCTION IN PREGNANCY COMPLICATED BY ACUTE POLIOMYELITIS

FREDERICK CARPENTER, M.D., F.A.C.S., MOSES COHEN, M.D., F.A.C.S., HENRY IRVING COLMAN, M.D., AND DAVID PLOTKIN, M.D., JAMAICA, N. Y.

(From the Department of Obstetrics and Gynecology, Queens General Hospital, Jamaica, New York)

WITH the rising incidence of poliomyelitis in the adult woman,[1] the management of pregnancy complicated by this condition has become an increasing problem to the obstetrician. In cases of acute respiratory paralysis, delivery of the patient has very often been accomplished by the hazardous procedure of removing the patient from the respirator.[2] This requires the establishing of an artificial airway. Often, a tracheotomy is performed. With the advent of Pitocin infusion, we have an alternative method by which labor can be induced. Delivery may then be accomplished without the removal of the patient from the respirator.

The following is a report of the management of a patient stricken with acute anterior poliomyelitis in the thirty-eighth week of gestation, further complicated by an acute fulminating toxemia which necessitated immediate delivery.

Case History

Mrs. L. F., a 20-year-old white primigravida, in the thirty-eighth week of gestation, was admitted to the Contagion Pavilion of the Queens General Hospital on Aug. 2, 1952. Her chief complaints were headaches, stiff neck, and weakness of the lower extremities of two days' duration. The patient appeared very acutely ill. Her temperature was 101° F., pulse 96, respirations 24, and blood pressure 130/80. Upon admission, the patient had moderate respiratory difficulty in the supine position. On the following day, there was progressive respiratory embarrassment due to the ascending involvement of the diaphragm, and the intercostal muscles up to the nipple line. It became necessary to place her in the Emerson respirator. The uterus was enlarged to the size of a thirty-eight weeks' gestation, with the breech in the fundus. The fetus was estimated to weigh about 5½ to 6 pounds. The fetal heart tones were audible in the left lower quadrant. At this time, laboratory findings were as follows: lumbar puncture: 194 cells per cubic millimeter with 119 lymphocytes, 66 polymorphonuclear leukocytes, protein 66 mg. per cent, cultures negative; hemogram: red blood cells 3.2 million, hemoglobin 10.0 Gm., white blood count 14,200, polymorphonuclear leukocytes 86 per cent, lymphocytes 14 per cent; urine: negative for albumin, glucose, acetone, and casts, specific gravity 1.017.

The primary concern upon admission was directed toward the treatment and management of the acute poliomyelitis. Delivery of the patient was to await the subsidence of the acute phase of the disease. On the day after admission, respiratory embarrassment continued and the patient now demonstrated weakness of the left upper extremity. Blood pressure at this time was 160/100. Urine now contained occasional granular casts. The patient exhibited two plus pitting edema of the lower extremities. A toxemia regime was instituted, consisting of hypertonic glucose administered intravenously, magnesium sulfate intramuscularly, and Luminal Sodium subcutaneously. Antibiotic therapy, which had been instituted upon admission, was continued. Sedation was modified because of the already existing severe respiratory depression.

After forty-eight hours of medical therapy for the toxemia, the patient began to complain of blurring of vision and severe headaches. Blood pressure had now risen to 164/120, with a 2 plus generalized edema, and a 4 plus albuminuria. Urine revealed a few hyaline and granular casts, and numerous white blood cells. Blood chlorides were 99 mg. per cent, carbon dioxide combining power 50 per cent, blood urea nitrogen 22 mg. per cent, uric acid 2.7 mg. per cent.

Because of the progression of the toxemia in spite of adequate therapy, immediate termination of the pregnancy was deemed necessary. Vaginal examination at this time revealed complete relaxation of the perineal muscles with the cervix fully effaced, 2 cm. dilated and soft. The vertex presented at minus 1 station in left occipitotransverse to left occipitoanterior position. The respiratory paralysis had progressed to the point where the patient could not tolerate being removed from the respirator.

An infusion consisting of 1 c.c. Pitocin in 1,000 c.c. of 5 per cent glucose in distilled water was started. Uterine contractions ensued almost immediately and progressed in frequency and duration. Within 3 hours, the cervix had become fully dilated and the head had descended to plus 3 station in left occipitoanterior position. After a second stage of 1½ hours, it became obvious that without the voluntary efforts of the paralyzed abdominal muscles, spontaneous delivery could not be effected. The instruments for delivery were introduced through the portholes of the respirator and a low forceps delivery under aseptic technique was accomplished without removal of the patient from the respirator. No episiotomy was needed and no lacerations were sustained. Oxygen was administered to the patient by mask and no intubation or tracheotomy was required. A female infant, weighing 5 pounds, 4 ounces, who breathed and cried spontaneously, was removed from the respirator in good condition. The placenta and membranes were delivered intact by modified Credé maneuver. The Pitocin infusion was allowed to continue and the uterus became firm, with a minimal amount of postpartum bleeding. One dose of ergonovine was given intramuscularly. The respiratory embarrassment of the patient appeared to be markedly improved immediately after delivery.

By the third day post partum, the blood pressure had fallen to 140/90; urine was negative for albumin and casts; the edema was subsiding. The patient was able to be removed from the respirator for the first time for 15-minute intervals without distress. The baby was discharged from the hospital in good condition on the tenth day, without any stigmas of poliomyelitis. The condition of the mother gradually improved except for an episode (2 months post partum) of paralytic ileus, secondary to renal calculi.

Comment and Conclusion

The preceding case exemplifies a method by which labor may be induced in a patient stricken with poliomyelitis of such a degree as to confine her to a respirator. Physiologists have demonstrated that the uterus will contract after division of the spinal cord as well as of its sympathetic nerve supply (Kleinberg and Horowitz[3]). The manner of response to an oxytocic agent such as Pitocin demonstrates beyond doubt that the uterus retains the intrinsic

ability to contract even in the presence of complete spinal paralysis. The relaxation of the cervix, vagina, and pelvic floor as a result of spinal paralysis often results in a short and relatively painless labor. In the case reported, the patient tolerated the procedure well, manifesting very little evidence of added discomfort as the result of the labor. After the presenting part has descended to the pelvic floor in the second stage of labor, the absence of adjuvant voluntary powers may necessitate the employment of some mechanical maneuver, such as manual extraction or forceps delivery.

This method does not, in itself, require the removal of the patient from the respirator, and the delivery may, in many cases, be readily performed by the operators working through the portholes of any standard tank-type respirator. Strauss and Bluestone[4] comment on the difficulties of vaginal delivery performed within the respirator, as it offers little opportunity for manipulation and asepsis due to the size of the chamber and the spacing of its portholes. It is their belief that breech extraction, forceps to the aftercoming head, episiotomy, manual removal of the placenta, repair of a lacerated cervix or perineum, and control of postpartum hemorrhage contraindicate this type of procedure. They further believe that alternating pressures of the chamber may be hazardous to the newborn and result in possible pulmonary or intracranial hemorrhage or air embolism. Certainly, in any instance where a difficult delivery is anticipated, such as in a primigravida with breech presentation or cephalopelvic disproportion, vaginal delivery in the respirator should not be attempted.

It is our belief, however, that manual extraction of a retained or adherent placenta can actually be performed with a minimal amount of difficulty through the portholes. With the complete relaxation of the birth canal due to the paralysis, extensive lacerations of the perineum, vagina, and cervix should rarely be encountered. Postpartum hemorrhage due to uterine atony can often be prevented by continuation of the Pitocin infusion. As far as the newborn is concerned, no ill effects were observed in our infant as a result of her brief stay in the pressure chamber. With due consideration given to these shortcomings, vaginal delivery in the respirator should be seriously considered before resorting to cesarean section.[5, 6] The latter procedure becomes much more formidable and hazardous because it entails the establishment of an endotracheal airway, with all its accompanying complications. Frequently, tracheotomy must be resorted to because of the subsequent laryngeal edema.

This case was further complicated by a toxemia of pregnancy which made it imperative to terminate the pregnancy. At times it is difficult to differentiate true toxemia from the arterial hypertension which is often seen in cases of bulbospinal paralysis. According to McDowell and Plum,[7] the appearance of hypertension in these patients may be the result of invasion of the brain-stem autonomic structure by the poliomyelitis virus. Edema and albuminuria are not uncommon findings in any patient confined to a respirator for any length of time. In spite of this diagnostic dilemma, when a patient demonstrates progressive hypertension, albuminuria, and edema, there is little alternative but to accept the diagnosis of toxemia of pregnancy and to institute

the usual medical regime. Due to the respiratory depression of these patients, the use of sedatives is limited and, if the patient fails to show improvement after adequate therapy, termination of the prgnancy becomes necessary. This is one of the many instances in which the use of Pitocin to induce labor should be considered before submitting the already acutely ill patient to the more formidable procedure of cesarean section.

Summary

1. A case of acute anterior bulbospinal poliomyelitis complicated by a fulminating toxemia of pregnancy is presented.

2. Termination of the pregnancy was effected by the use of Pitocin induction and forceps delivery accomplished within the respirator.

References

1. Bowers, V. M., and Danforth, D. N.: Am. J. Obst. & Gynec. **65**: 34, 1953.
2. Nelson, R. B., and Johnson, K. W.: Am. J. Obst. & Gynec. **65**: 431, 1953.
3. Kleinberg, S., and Horowitz, T.: Surg., Gynec. & Obst. **72**: 58, 1941.
4. Strauss, H., and Bluestone, S. S.: Am. J. Obst. & Gynec. **51**: 114, 120, 1946.
5. Horn, P.: Ann. West. Med. & Surg. **5**: 93, 1951.
6. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc., p. 737.
7. McDowell, F. H., and Plum, F.: New England J. Med. **245**: 241, 1951.

BILATERAL AGENESIS OF THE KIDNEYS IN TWO CONSECUTIVE INFANTS

CHARLES BARON, M.D., COVINGTON, KY.

(From the Department of Obstetrics and the Department of Pathology, St. Elizabeth Hospital)

THIS is the second time in a practice of twenty-two years that I[1] have been able to observe and record in the world literature a unique experience.

Macht[2] in 1950 reported that his search of the literature revealed 168 cases of bilateral agenesis of the kindeys, while Leffler[3] in 1951 stated that his search revealed 163 cases. Since Everhard,[2] quoted by Macht, reported his first case in 1633, no instance has been reported of two such cases occurring in two consecutive pregnancies. A search of the extensive literature revealed, however, in a report by Madisson,[4] four cases where two such pregnancies occurred in the same mother but not consecutively. In this instance, the mother's first pregnancy resulted in the birth of a 7 months' male fetus that lived 16 days and the cause of death was unknown. The second pregnancy resulted in the birth of a 7 month stillborn male fetus, that on autopsy was found to have bilateral agenesis of the kidneys. The third pregnancy resulted in a full-term normal girl. The fourth pregnancy resulted in a full-term male child that lived 25 minutes and on autopsy was found to have bilateral agenesis of the kidneys.

The incidence of this condition is variable depending on the criteria used. Allen[5] quotes Bell as finding 7 in 2,400 stillbirths, or 1 in 343. Potter[6] reports 30 in over 5,000 autopsies, while Nation[7] reports 3 in 27,000 autopsies.

My two cases were both in males, which coincides with the predominance of this condition in males as presented in other larger series. In Potter's[6] series of 30, only 4 were females, while Allen[5] states that it occurs in a ratio of about 2½ to 1.

I agree with Amolsch[8] in supporting the theory that germ plasm deficiency is the factor responsible for anephrogenesis. "The germ plasm defect may be hereditary but more likely the deficiency is occasional and dependent on circumstances influencing the maturation and fertilization of gametes. Therefore, most instances of renal agenesis are congerminal or congential in genesis." To support the occasional circumstance Macht[2] reports "cases in which only one twin had been found to have renal agenesis." However, he does not state whether these occurred in heterozygous or homologous twins.

In my case, I had already delivered the mother of one full-term healthy boy, yet two subsequent consecutive pregnancies resulted in the cases reported in this paper. In Madisson's report of two siblings born with bilateral agenesis of the kidneys, this occurred in the second and fourth pregnancies.

Smith,[9] in his report of a case, stated that "the prognosis for future pregnancies where the mother had a child with this abnormality appears to be excellent." In Madisson's[4] instance and in mine this did not hold true. I will have to admit that after the first instance in my patient, I was asked this very question and in all confidence I encouraged the patient to become pregnant again. By a strange coincidence, the father of these children had had a kidney removed because of a hydronephrosis due to pressure of an aberrant blood vessel on Jan. 1, 1951, just a short while before the conception of the first abnormal child.

The best description of bilateral agenesis of the kidneys is given by Potter[6] as follows:

"This malformation is much more common than is generally believed. Thirty infants with complete absence of kidney tissue are included in the Chicago Lying-in Hospital series of autopsies on fetuses and infants.

"The condition is confined largely to males; among 30 infants observed, only four were females. In three the uterus and vagina were absent, although the fallopian tubes and ovaries were normally developed. In the fourth the uterus was present and the upper part of the vagina formed a small sac enclosing the lower end of the cervix. The lower part of the vagina was absent. The extent of associated malformations varies greatly in both sexes. In 20 cases previously reported, five infants were otherwise normal, three were normal except for clubfoot, seven had multiple anomalies of the central nervous system or skeleton and four had malformations limited to the heart or intestinal tract. Sympodial monsters are usually without kidneys and although only one was present in the group reported, several have been observed since then.

"Bilateral renal agenesis is accompanied by sufficiently characteristic changes to permit diagnosis of the kidney condition from inspection of the head. The ears are abnormally soft and flat owing to poor development of cartilage. They are unusually large, are placed low on the head and are often less upright than normal. The space between the eyes is somewhat increased, the line of the palpebral fissures is either unusually flat or is higher at the outer than at the inner canthus and a prominent epicanthic fold forms a wide semicircle at each side of the nose and covers the medial palpebral commissure.

"Intrauterine life does not appear to be hampered by the absence of kidneys, for many of these infants are born normally at term. Because waste products are successfully eliminated via the placenta, urinary secretion is not necessary to maintain intrauterine life. The longest survival in our series was 11 hours. Death of all the liveborn infants was preceded by dyspnea, cyanosis and evidence of respiratory embarrassment. The lungs of all were hypoplastic, and this pulmonary abnormality was fatal before the absence of the kidneys could cause death from uremia.

"The abnormality appears to be due either to failure of the mesonephric ducts to extend down to the area from which the metanephric buds ordinarily arise or to a secondary degeneration of this region after the mesonephric ducts

have been formed. The Müllerian ducts, which lie immediately adjacent to the mesonephric ducts, are also affected, the lower portions failing to develop or undergoing degeneration simultaneously with the mesonephric ducts. Although the fallopian tubes are normal, the uterus, corpus and major portion of the vagina are usually absent. Adrenal glands and gonads are normally developed, although the former remain flat oval discs against the posterior abdominal wall since in the absence of kidney tissue there is nothing to compress them into their usual shape.

"The bladder fails to become differentiated and is only a thin tubelike structure extending from the urethra to the internal umbilical ring."

Case Report

The mother was a 23-year-old para i, gravida ii, with a normal living child. Her health was good and there was no history of any illness. She was 8 months pregnant when she was admitted to the hospital on Jan. 29, 1952, with intact membranes. After admission, complete dilatation of the cervix was followed by spontaneous delivery of a male infant with a midline episiotomy. The placenta was delivered intact. The amount of amniotic fluid was not recorded.

The baby cried after 15 minutes. He was cyanotic and respirations were poor. Oxygen was given but he remained cyanotic and the respirations did not improve. The trachea was aspirated several times and a small amount of mucus was obtained. The baby died nine hours after delivery.

The following is the pertinent material from the necropsy report by Dr. Robert Ritterhoff of St. Elizabeth Hospital: The body weighed 2,200 grams and measured 45 cm. in length. The foramen ovale and ductus arteriosus were patent. The cardiac chambers appeared to be normal. There was a complete absence of both kidneys and ureters. The bladder was of decreased size and measured approximately 1 cm. in diameter. Microscopic examination of the lung tissue showed hyaline-membrane formation.

The clinical diagnosis was probable hyaline membrane and possible cerebral hemorrhage. The anatomical diagnosis was (1) absence of both kidneys and ureters; (2) hypoplasia of the urinary bladder; (3) atelectasis of both lungs; (4) patent foramen ovale and ductus arteriosus; (5) facies renalis.

The second infant, another boy, was delivered on April 27, 1953, at 12:45 P.M. As in the first instance, the amount of amniotic fluid was not recorded. This baby's birth weight was 5 pounds, 4½ ounces. He also was cyanotic. Respirations were delayed approximately ten minutes and the cry was also delayed. The baby was given oxygen, Coramine, and resuscitation. In the next hour the respirations became more and more labored and retractions were very deep. Caffeine, 0.5 c.c., was given at 1:20 P.M. and again at 1:45 P.M. The baby died 2 hours and 25 minutes after birth.

The following is the pertinent material from the necropsy report by Dr. K. Stemzer of St. Elizabeth Hospital. Tne body, 42 cm. in length and 2,250 grams in weight, was that of a well-developed newborn male infant. The ears were normally soft and unusually large. The space between the eyes was somewhat increased. There were a prominent epicanthic fold and wide semicircle at each side of the nose. The tip of the nose was slightly flattened. The foramen ovale was open and the ductus arteriosus was patent. Both kidneys were absent. The ureters were not seen. The urinary bladder was very small and was only a thin tubelike structure extending from the urethra to the internal umbilical ring. The urethra was patent. The left testicle was in the abdomen and the right testicle lay in a channel. Both were of normal appearance. The suprarenal glands were somewhat flattened and enlarged. They presented on section normal relationship between the cortical and medullary tissue.

The anatomical diagnosis was (1) marked mediastinal and interstitial pulmonary emphysema; (2) agenesis of both kidneys and ureters; (3) typical features of the face in kidney agenesis; (4) hypoplasia of the urinary bladder; (5) milia in the skin of the forehead; (6) slight meningeal edema.

Conclusions

1. This is the first reported instance in the literature of two consecutive cases of agenesis of both kidneys in the infants of one mother.

2. This is the second reported instance of two such cases occurring in siblings.

References

1. Baron, Charles: J. A. M. A. **102**: 1675, 1934.
2. Macht, Allan H.: Am. J. Dis. Child. **80**: 297, 1950.
3. Leffler, R. J.: Am. J. Clin. Path. **21**: 752, 1951.
4. Madisson, H.: Centralbl. f. allg. Path. u. Path. Anat. **60**: 1, 1934.
5. Allen, A. C.: The Kidney, New York, 1951, Grune & Stratton.
6. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, 1952, The Year Book Publishers.
7. Nation, E. F.: Surg., Gynec. & Obst. **79**: 175, 1944.
8. Amolsch, A. L.: J. Urol. **38**: 360, 1937.
9. Smith, H. G.: Canad. M. A. J. **65**: 148, 1951.

SUBPUBIC IMPACTION OF A POSTPARTUM UTERUS

WILLIAM C. BECK, M.D., JOHN H. FEIST, M.D., AND RALPH M. SCOTT, M.D.
SAYRE, PA.

(From the Sections on Surgery and Obstetrics at the Guthrie Clinic and Robert Packer Hospital)

WHILE impaction of retroverted uteri has been occasionally mentioned in the literature, a retropubic impaction with anteversion is certainly rare. The following case is reported as an example. A nearly exhaustive search of the literature has failed to reveal any similar instance.

Case Report

A primipara, 20 years old, was seen as an emergency case on the fifth day following delivery. Her pregnancy, delivery, and postpartum course prior to the present incident had been entirely uneventful. The delivery was a spontaneous left occipitoanterior aided by a left mediolateral episiotomy. During the puerperium the uterus involuted satisfactorily and the patient was ambulatory on the second day.

On the fifth postpartum day the patient felt fine but as she returned from the washroom and as she stooped forward and raised herself on tiptoe in order to sit on the edge of her bed, she suddenly experienced a severe stabbing suprapubic pain which doubled her up and momentarily "took her breath away." She managed to lie down and felt most comfortable in a lateral decubitus position with knees drawn up. The pain was constant and increased steadily in intensity. Soon the patient felt nauseated but did not vomit. She had had a spontaneous normal bowel movement just prior to this incident. Her pulse rate had increased from 70 to 110. Her temperature remained normal. The respiratory rate increased from 18 to 24 and the respirations were shallow. The lochia on the preceding day had been of normal amount and serosanguineous in character. Lochia prior to the incident was nil and the patient had noticed only slight serosanguineous spotting when she first arose in the morning. The character of the pain was at first steady and knifelike but soon became crampy and aching in character, resembling labor pains, but without pain-free intervals.

Inquiry into her previous history and systemic review revealed nothing contributory except that a Gilliam type hysteropexy had been performed one year previously for the relief of symptomatic uterine retroversion and primary infertility.

Physical examination was entirely normal with the exception of the abdominal and pelvic findings. The abdomen was soft and flat. There were no palpable organs or masses and the previously palpated puerperal uterus could no longer be felt. (On the preceding day the fundus was hard and extended to 10 cm. above the symphysis.) There was exquisite tenderness in the midline just above the symphysis and nowhere else. Percussion and rebound tenderness were severe but confined to this small area. Peristalsis was diminished. Abdominal wall cutaneous reflexes were normal. There was no costovertebral angle tenderness. The patient at that time complained of radiation of the pain to the lower lumbar region in the midline but no tenderness could be elicited there. There was a well-healed oblique right lower quadrant incision. Following shaving and cleansing of the perineum, an aseptic vaginal examination was undertaken. The uterine fundus was found impacted beneath the symphysis pubis and only the anterior wall of the uterus was available for palpation. The cervix was presumed to be located in a craniodorsal direction. Both cornua of the uterus were tense and tender (Fig. 1).

On the basis of these findings it was felt that the involuting uterus had become excessively anteverted and the fundus impacted beneath the symphysis pubis with the Gilliam

suspension acting as a fulcrum. The degree of anteversion from the normal position was estimated to be approximately 145 degrees.

A bimanual procedure was then carried out in two stages. First, the fundus was depressed by both hands and released from beneath the symphysis pubis and was pushed craniad until it was easily palpable by the abdominal hand. As soon as this was accomplished the patient volunteered the information that she had experienced almost total relief from her acute anterior pain but the pain in the lower lumbar area still persisted. It was now possible to locate the cervix. The posterior cervical lip bore an edematous rim permitting a secure grip upon it and the cervix was thereby pulled downward with simultaneous upward pressure upon the fundus by the abdominal hand. As soon as the uterus was restored to its normal inclination it was then pushed up out of the pelvis and remained there without difficulty. At this time the patient was completely and dramatically relieved of all pain. The pulse and respiratory rates returned to normal and there was no longer any tenderness. Immediately upon return of the uterus to its normal position a fairly large amount of mucus and serosanguineous lochia was expelled.

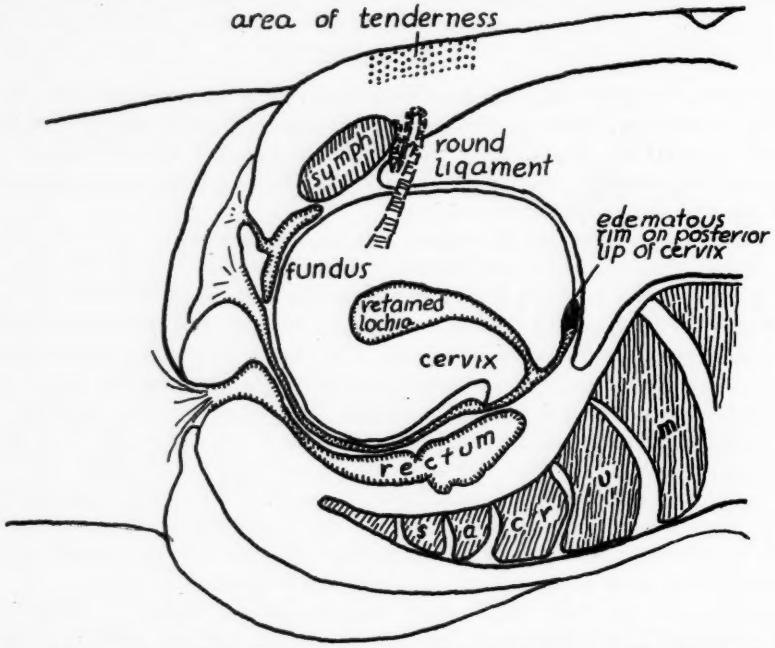


Fig. 1.—Schematic cross section of pelvis at initial examination. (Hypothetical position of round ligaments shown in interrupted lines.)

The patient thereafter remained asymptomatic and afebrile and resumed the course of a normal puerperium. The episiotomy repair had not been disturbed and follow-up examination disclosed no abnormalities. The semi-involuted uterus remained in proper position and the flow of lochia, once re-established, continued in the usual fashion.

Conclusion and Summary

A rare complication of the puerperium has been reported in a young white primipara with a previous Gilliam type hysteropexy. On the fifth postpartum day, the uterus had become acutely impacted beneath the symphysis after having rotated ventrad over an arc of about 145 degrees. The condition was diagnosed with ease and the uterus replaced in its normal position by a two-stage bimanual maneuver. This resulted in dramatic, instantaneous, and complete relief of all symptoms and positive physical findings and in resumption of the lochial flow.

STEVENS-JOHNSON SYNDROME IN PREGNANCY

HERBERT G. WINSTON, M.D.,* AND LUIGI MASTROIANNI, JR., M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York Medical College, and the Division of Obstetrics and Gynecology of Metropolitan Hospital, New York)

STEVENS and Johnson,[1] in 1922, described a new eruptive fever. This was characterized by a skin eruption with ulcerative stomatitis, conjunctivitis, balanitis, and severe constitutional symptomatology. Similar cases have been described by others, being variously referred to as dermatostomatosis, ectodermosis erosiva pluriorificialis, and erythema multiforme exudativum. The condition has now generally come to be known as Stevens-Johnson syndrome.

Our case is believed to be the first reported case of pregnancy complicated by this condition. The patient presented a classical picture of the entity. A unique feature, however, is that there was complete obliteration of the vagina secondary to ulcerative mucous membrane lesions.

Case Report

M. W., a 30-year-old Negro primigravida, was admitted to the medical service of the Metropolitan Hospital on May 22, 1952, complaining of a severe sore throat, pruritic skin eruption, and fever. Thirty months prior to hospital admittance she had been given a course of penicillin injections for syphilis. Since that time she had received occasional penicillin injections for upper respiratory infections, the last of these having been given two weeks before the onset of the present illness. Three days prior to admittance she experienced generalized malaise, and awoke the next day with a sore throat and swollen eyelids. At this time she noted pain in the extremities and that she had swollen and ulcerated lips. She was again given penicillin by her physician for these symptoms. The sore throat became increasingly severe, interfering with speech and swallowing, and the eyelids became progressively more painful and swollen. She sought admittance to the hospital because she felt too ill to be cared for at home.

Her last normal menstrual period had occurred some time in November, 1951, placing her between the sixth and seventh months of pregnancy. Her antepartum course, though unsupervised, had been unremarkable until the onset of this present illness.

Physical examination revealed an acutely ill Negro woman who was unable to give much of a history because of marked edema of the throat, oral cavity, and lips. Her temperature was 104° F. rectally; blood pressure was 140/90 mm. Hg. The eyelids were swollen and a crusted exudate was present. The conjunctivae were injected. There was an erythematous vesicular eruption over the cheeks and nose, and a violaceous papuloannular eruption over the back and extremities. The lips were edematous, cracked, and ulcerated. The tongue was thick and swollen. The mucosa of the oropharynx was red and scattered necrotic patches were present upon the fauces and uvula. Several tender plum-sized anterior cervical lymph nodes were palpable. Moist râles and coarse rhonchi were heard throughout the lung fields. The uterus was enlarged to approximately twenty-six weeks' size. Fetal heart sounds were regular and strong. Laboratory studies were reported as follows: hemoglobin 11 Gm. per

*Present address: Capt. Herbert G. Winston, M.C., United States Army Hospital, Fort Jay, Governors Island, New York 4, N. Y.

cent, white blood cell count 22,100 with 33 per cent neutrophils, 60 per cent lymphocytes, 6 per cent monocytes, and 1 per cent basophils; the Mazzini test was two plus; the cephalin-flocculation test was negative; the total protein was 5.6 Gm. per cent with albumin 3.4 Gm. per cent and globulin 2.2 Gm. per cent; the chest film revealed an area of mottled density in the right middle lobe; and the conjunctival culture revealed diphtheroids. The remainder of the laboratory studies were found within normal range.

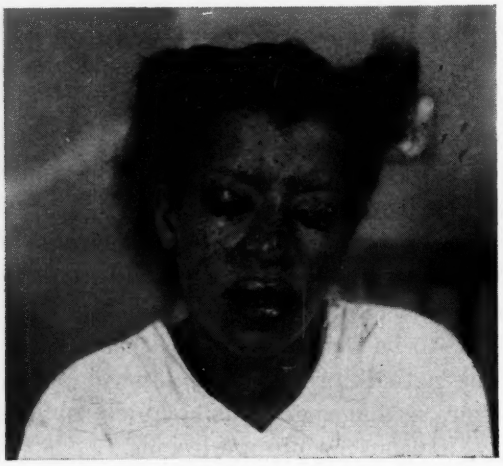


Fig. 1.—Taken before ACTH therapy, showing typical lesions of face, eyes, and lips.

A diagnosis of Stevens-Johnson syndrome was made and penicillin sensitivity was considered as the etiological basis. The patient was placed upon a regimen including aureomycin, antihistaminics, parenteral fluids, and soothing mouth rinses. Over the next two days she ran a septic course with spikes of fever to 104° F. She was unable to swallow and parenteral fluids were continued. The skin over the entire body became covered with the papulovesicular eruptions, more marked on the face and trunk. The lips and oral mucosa remained ulcerated. On the third hospital day, ACTH, 25 mg. every six hours, was instituted. The following day, the patient's condition was much improved; the periorbital and oral edema lessened, pruritus disappeared, and the skin lesions appeared less angry looking. Gradual continued improvement in the skin lesions occurred; the fever abated; the conjunctivae were less inflamed but the damage to the cornea was feared to be permanent. On the thirty-second hospital day, the patient experienced a moderately severe asthmatic attack despite the continued use of ACTH. Aminophylline intravenously controlled this episode. Repeated asthmatic attacks occurred at frequent intervals and were partially but not completely controlled. On the thirty-seventh day she went into labor spontaneously and was transferred to the obstetrical service. She became severely orthopneic and severe asthmatic attacks required frequent administration of intravenous aminophylline. Continuous oxygen via nasal catheter was given. The progress of labor was followed by rectal examination and immediately on full dilatation she was taken to the delivery room. On attempted vaginal examination at this time, it was noted, with consternation, that the vagina was completely obliterated from the level of the hymenal ring up to the level of the presenting vertex which was at station zero. Cesarean section as a method of delivery could not be considered because of the severe orthopnea, the presence of the rather extensive abdominal skin lesions, and the development of strong second-stage uterine contractions. Immediate delivery was demanded lest severe damage occur with rupture of the vagina and/or contiguous organs. Pudendal block anesthesia was effected, a catheter was placed into the bladder, and an assistant's finger inserted into the rectum. With the labia retracted, a transverse incision was made into the now bulging dome of the obliterated vagina and continued upward by sharp and blunt dissection until the amniotic sac was

incised; a vertical extension inferiorly was now made and carried into a deep right mediolateral episiotomy. Spontaneous delivery of a living 1,989 gram male infant occurred immediately thereafter. Placenta and membranes were delivered intact by Brandt-Andrews maneuver with minimal blood loss. The vagina and episiotomy were then repaired so as to fashion a patent vaginal tube. A petrolatum gauze packing was placed to prevent recurrence of the obliteration. The postpartum course was obstetrically benign and the asthma was improved but still present.

Fig. 2.—One month post partum after ACTH therapy. Note resolution of lesions of skin and lips; keratitis and conjunctivitis have persisted.

Over the next month the skin lesions gradually healed, leaving areas of hyperpigmentation. The keratitis and conjunctivitis had improved, but vision was markedly impaired due to corneal scarring. The respiratory difficulty continued and repeated bouts of asthma and bronchitis necessitated intermittent therapy with ACTH, cortisone, compound F, and antibiotics. Six months following delivery the patient was still in the hospital. A bronchographic study revealed fairly marked bronchiectasis. A vaginal examination performed during this period revealed a well-formed introitus and vagina. At the time of this report, the patient is still hospitalized principally because of the respiratory residuum and her prognosis is considered poor. The baby had a completely uneventful neonatal period and is a healthy normal 1-year-old boy at the present time.

Comment

About one-fourth of the well over 100 cases of Stevens-Johnson syndrome reported in the literature were in females. Of these, vulval and/or vaginal involvement is reported in only seven.[2, 3, 4, 5] The extent of involvement is not mentioned in any of these cases. The vaginal lesions are similar to those involving the mouth, pharynx, and lips. They are vesicles or bullae on an erythematous base which become ulcerated. In our case there was coalescence of the lesions and, on healing, obliteration of the vagina.

Ashby and Lazar,[6] in an excellent review of the subject, have summarized the salient features of the disease. They describe prodromas of malaise, fever, and sore throat. Stomatitis is seen in every case. Purulent conjunctivitis is usually present with occasional corneal involvement. Over half of the cases reported in males showed penile lesions. The skin lesions are multiform, being

erythematous, vesicular, and bullous. There is lung involvement in about one-third of the cases. The mortality rate in Ashby and Lazar's 77 collected cases was 10 per cent.

The etiology of Stevens-Johnson syndrome is unknown. The consensus is that it is allergic in nature. In many of the reported cases, its onset follows penicillin or sulfonamide therapy, but these drugs may have been administered to treat the prodromas of the already existing disease and hence were probably not causative. Recently, ACTH and cortisone have yielded good results.[7, 8]

Stevens-Johnson syndrome has not been mentioned in the literature among the factors producing vaginal atresia. Caustic douches, trauma, and infections, specifically typhoid fever, diphtheria, and smallpox, are most commonly cited as causative.

The management of atresia of the vagina complicating pregnancy has been outlined by Piklamaa.[9] He does not believe that the atresia should be treated during pregnancy because of the hyperemia that is present and also because of the danger of infection. If a thin membrane is present, it should be incised at delivery, but if the obliteration is more extensive, he advises cesarean section with drainage of the uterus through the abdomen. In our case, the vaginal obliteration was unrecognized until full cervical dilatation. Because of the severe orthopnea necessitating the maintenance of high Fowler position and also because of the presence of extensive skin lesions, delivery by cesarean section could not be considered.

Summary

1. The entity of Stevens-Johnson syndrome is described and the literature is reviewed.

2. Vaginal obliteration complicating pregnancy is discussed.

3. A case exhibiting both of these complications is presented.

4. This is believed to be the first report of the concurrence of pregnancy with Stevens-Johnson syndrome.

5. Likewise a new etiological factor responsible for obliteration of the vagina is demonstrated.

6. The effectiveness of ACTH therapy in this condition is further documented.

References

1. Stevens, A. M., and Johnson, F. C.: Am. J. Dis. Child. 24: 526, 1922.
2. Fletcher, M. W. C., and Harris, R. C.: J. Pediat. 27: 465, 1945.
3. Dardinski, V. J.: Am. J. Clin. Path. 15: 28, 1945.
4. Ageloff, H.: New England J. Med. 223: 217, 1940.
5. Mecklin, B., and Saunder, W.: New York State J. Med. 52: 1447, 1952.
6. Ashby, D. W., and Lazar, T.: Lancet 1: 1091, 1951.
7. Wammock, V. S., Biederman, A. A., and Jordan, R. S.: J. A. M. A. 147: 637, 1951.
8. Agostas, W. N., Reeves, W., Shanks, E. D., and Sydenstricker, V. P.: New England J. Med. 246: 217, 1952.
9. Piklamaa, A.: Acta obst. et gynec. Scandinav. 29: 47, 1949.

TONIC CONVULSIONS AND CARDIOVASCULAR COLLAPSE FOLLOWING AN INJECTION OF PROSTIGMIN

T. M. WILSON, M.D., WASHINGTON, D. C.

EXTENSIVE reports have been published on the use of cholinergic drugs to evoke menstruation in the absence of organic disease or pregnancy. However, none of the authors mention any serious side effects. It is the purpose of this paper to report one case of tonic convulsions and cardiovascular collapse following a single 1.0 mg. intramuscular injection of Prostigmin.

Decker[1] reported "no toxic effects or side effects" in a series of 101 cases, even using such large amounts as 2.0 mg. of Stigmonene. Hinman and Roby,[2] in a series of Prostigmin tolerance trials in 70 patients, stated that there were no objective signs and the only subjective symptoms were slight dizziness, headache, nausea and vomiting, salivation, and diarrhea. Thick tongue and difficulty of speech of a transient nature were noted in two cases. Soskin and associates[3] reported no unpleasant subjective or objective effects from Prostigmin in 50 patients. Carapetyan,[4] Thelen,[5] Parella,[6] Douglas,[7] and Sneider[8] in their series of cases reported no toxic effects from Prostigmin therapy.

We have been using Prostigmin in 0.5 and 1.0 mg. doses intramuscularly for three successive days for eliciting menstrual flow in those patients who have amenorrhea with no demonstrable organic pathology, in those patients who have amenorrhea for eight or more weeks post partum (not lactating), and occasionally for the diagnosis of early pregnancy. It has been our impression that many patients with delayed menstruation become emotionally upset over fear of pregnancy, and this anxiety may cause a "sympathetic blockade" of the acetylcholine necessary for uterine vasodilation and hyperemia necessary for the onset of menstruation. This may, in turn, prolong the amenorrhea. Prostigmin inhibits cholinesterase, the tissue enzyme which destroys acetylcholine[3, 4]

Case Report

A 25-year-old gravida i, para i, twelve weeks post partum and eight weeks after cessation of lactation was seen for amenorrhea. There was no history of allergy. She was given 1.0 mg. of Prostigmin intramuscularly and told to report back on the following two days for repeated treatment. About twenty minutes after leaving the office, she staggered back into the reception room, speechless and struggling for breath. The skin was ashen in color. The blood pressure was 60/40, and the pulse 40, slow and regular. The lungs were clear, and the heart sounds were normal except for the bradycardia.

Almost immediately after her return to the office, the patient went into a tonic convulsion with opisthotonus. Respirations ceased, and the pulse was barely perceptible. Five-tenths c.c. of epinephrine 1:1,000 was given three times over a few minutes, but the patient went into the seizures every three to four minutes.

Atropine 0.4 mg. was also given intramuscularly and finally intravenously. The seizures became less severe and further apart, but still occurred. The patient had approximately ten seizures.

A hurried telephone consultation with an internist resulted in giving the patient 10 c.c. of 10 per cent calcium gluconate intravenously with immediate cessation of the convulsions.

A careful history taken after the convulsions revealed no previous convulsions, no previously known drug sensitivities, and no allergies. Medical history was negative. The patient had never previously received any cholinergic drugs.

This dramatic (and nerve-shattering) experience has taught me that apparently nontoxic drugs should be treated with respect, and antidotes for such drugs should be on hand and their use familiar to the practitioner.

References

1. Decker, A.: Am. J. Obst. & Gynec. **64**: 1137, 1952.
2. Hinman, C. H., and Roby, C. C.: Am. J. Obst. & Gynec. **57**: 586, 1949.
3. Soskin, S., Wachtel, H., and Hechter, O.: J. A. M. A. **114**: 2090, 1940.
4. Carapetyan, H.: J. A. M. A. **122**: 81, 1943.
5. Thelen, C.: Jackson Clin. Bull. **10**: 126, 1948.
6. Parrella, D.: West. J. Surg. **54**: 397, 1946.
7. Douglas, H. S.: West. J. Surg. **51**: 245, 1943.
8. Sneider, M. J.: Illinois M. J. **83**: 107, 1943.

1673 Columbia Road, N. W.

THE YOUNGEST PATIENT WITH A GRANULOSA-CELL TUMOR

JEHAN SHAH SALEH, M.D.,* TEHERAN, IRAN

IN THE last decade great interest has been aroused in an endocrine group of ovarian tumors, mainly "granulosa-cell tumors." This tumor arises from early oophorogenic structures in the sex gland area and produces estrin which is responsible for premature development of the secondary sex characteristics in children, with the appearance of menstruation. In adult life there is prolonged bleeding, and in the menopause return of menstruation while the atrophic uterus resumes its normal size.

Although granulosa-cell tumors are not uncommon and are encountered at any age from infancy to the senium, our patient is the youngest so far reported in the literature, being only 2 years and 8 months old. Bland and Goldstein reported a granulosa-cell tumor in a child of 7 years with precocious menstruation. Kleine has reported a similar case in a patient 3½ years old.

Case Report

On May 25, 1952, a disturbed mother with a child 32 months old consulted me at the Hemayat-Madran Hospital. She stated that the child had been menstruating irregularly for the past 4 months, and that the family was extremely worried about this most abnormal situation.

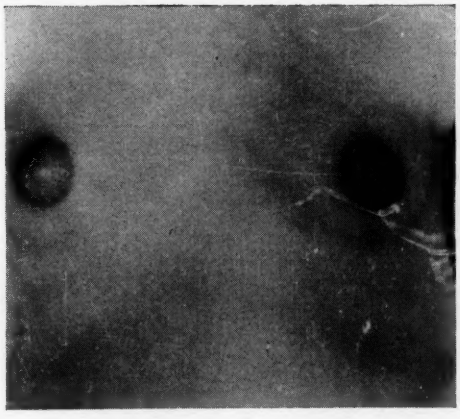


Fig. 1.—The breasts are fully developed.

On examination, the child looked anxious and self-conscious. Although the physical make-up of the child appeared to be older than 32 months, her mental age and activities were not in advance of her years. Breasts were fully developed (Fig. 1), and the distribution of hair in the pubic area was quite marked and feminine, and there was slight growth of hair in the axillary region. The lower abdomen was enlarged, especially so on the left side. The genitals were those of a mature girl in appearance, and there was a slight bloody discharge. Rectal examination revealed a small uterus and a large mobile tumor in the left adnexa. General examination was otherwise normal.

*Professor of Gynecology, Dean, Teheran University Faculty of Medicine.

Fig. 2.—Spherical tumor of the size of a child's head with a well-developed capsule.

Fig. 3.

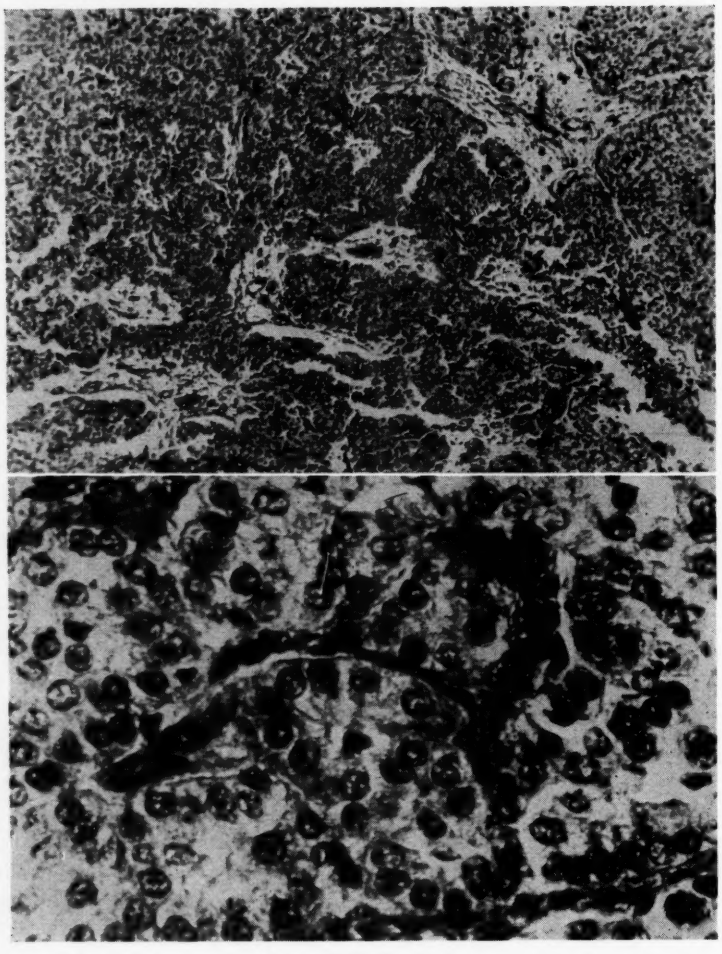


Fig. 4.

Fig. 3.—The cells are arranged in trabeculae. The connective tissue traverses the tumor in bands, dividing the cellular zones into large and small lobules.

Fig. 4.—The tumor cells in places are distributed radially about clear spaces, but no vacuoles similar to Call-Exner bodies are noticed.

Considering the clinical aspects of the case, a tentative diagnosis of a granulosa-cell tumor was made and the patient was operated upon the next day under general anesthesia. Exploration of the pelvis revealed a small uterus in anteflexion with a large ovarian tumor on the left side. The right adnexa were normal. The tumor had a small pedicle and was easily removed, and the abdomen closed in the usual manner. Following is the report received from Dr. Rahmatian, Associate Professor, Department of Pathology.

Pathological Anatomy.—Gross: The tumor was spherical in shape, the size being that of a child's head. The surface was rounded and smooth and bossed in only two places. Its consistency was rather soft and it had a well-developed capsule. On section the cut surface was cellular, resembling marrow, and had a yellowish tint with hemorrhagic spots dispersed throughout (Fig. 2).

Microscopic: The tumor cells were variable, round and polygonal in places, the nuclei either vesicular or irregular, but well stained. The nuclei contained a finely granular nucleolus. The cells were arranged in trabeculae, and in places solid masses were seen with a tendency toward rosette formation. The tumor cells in places were distributed radially about clear spaces, but no vacuoles similar to Call-Exner bodies were noticed. The connective tissue traversed the tumor in bands, dividing the cellular zones into large and small lobules, which in turn were subdivided by hyaline connective tissue. Degenerative changes, such as hemorrhage and necrosis, were encountered. Large pale-staining polygonal cells which resembled lutein cells were seen here and there. These large cells may represent a luteinization of the granulosa cells. The epithelioid cells contained fat droplets (Figs. 3 and 4).

Postoperative Course: The patient recovered in ten days and was discharged from the hospital. She was seen twice after the operation. The precocious menstruation had ceased and the breasts were rapidly becoming flat. The hair had entirely disappeared from the axillary region and was almost gone from the pubic areas.

On the last visit, she was urged to have a picture taken for comparison with the ones taken preoperatively, but she has not presented herself in spite of the promises made by the mother. We are still hopeful of showing the postoperative pictures, because the child has unfortunately developed a small postoperative ventral hernia, and will most probably come again to have the necessary repair done.

References

Bland, P. B., and Goldstein, L.: Surg., Gynec. & Obst. **61**: 250, 1935.
Burrows, H.: Biological Actions of Sex Hormones, London, 1945, Cambridge University Press.
Danforth, D. N.: AM. J. OBST. & GYNEC. **43**: 984, 1942.
Dockerty, M. B.: AM. J. OBST. & GYNEC. **39**: 434, 1940.
Geist, S. H.: Ovarian Tumors, New York, 1942, Paul B. Hoeber, Inc.
Henderson, D. N.: AM. J. OBST. & GYNEC. **43**: 194, 1942.
Meyer, R.: AM. J. OBST. & GYNEC. **22**: 697, 1931.
Novak, E.: Gynecological and Ostetrical Pathology, Philadelphia, 1941, W. B. Saunders Company.
Traut, H. F., and Marchetti, A. A.: Surg., Gynec. & Obst. **70**: 632, 1940.
Willis, R. A.: The Spread of Tumours in the Human Body, London, 1934, J. & A. Churchill, Ltd.
Willis, R. A.: Pathology of Tumours, London, 1948, Butterworth & Co., Ltd.

A THIRTEEN-SOMITE PREGNANCY ON THE SURFACE OF THE OVARY

J. D. O'KEEFE, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital)

IN 1878 Spiegelberg published his four criteria which have become basic for the diagnosis of true ovarian pregnancy. They are: (1) the tube, including the fimbria, must be intact and must be distinctly separate from the ovary; (2) the gestational sac must definitely occupy the normal position of the ovary; (3) the gestational sac must be connected to the uterus by the uterovarian ligament; and (4) unquestionable ovarian tissue must be demonstrated in the walls of the sac. In the case presented, the fourth criterion as modified by Stander is not fulfilled. The Fallopian tube was so definitely normal it was not removed at the time of operation; thus the modification of Spiegelberg's first criterion by Norris is not fulfilled.

B. M. (No. 529371), a 27-year-old gravida iii, para 0, white patient had been seen at regular intervals over a period of six months complaining of dyspareunia, dysmenorrhea, and intermittent lower abdominal cramps. She was seen in the hospital emergency room on Dec. 12, 1951, because of an increased severity of these lower abdominal cramps with a sharp pain in the rectum and weakness over the previous twenty-four hours. Her last menstrual period had been on Nov. 13, 1951, and there had been no vaginal bleeding, nausea, vomiting, breast tenderness, fainting, chills or fever. Physical examination revealed a pulse of 116, a blood pressure of 130/70, a temperature of 37.7° C., and respirations of 18 per minute. The patient appeared pale and in slight distress but alert and cooperative. The heart and lungs were normal. The abdomen was soft, not distended, and the bowel sounds were normal. There was mild tenderness to deep palpation in the midline of the lower abdomen but no rebound tenderness was noted. The uterus was forward and at the upper limits of normal size. In the region of the left adnexa was a 2 by 2 by 3 cm. soft, exquisitely tender mass. The right adnexa were negative. There was slight tenderness with motion of the cervix and it appeared almost multiparous, with a polyplike structure protruding through the external os with a small amount of bright red bleeding. The hematocrit was 38 volumes per cent, the leucocyte count was 15,350 per cubic millimeter, and the urine examination was negative. The patient was admitted to the hospital for observation with a diagnosis of possible ectopic pregnancy or pelvic inflammatory disease.

The next morning at 4:30 A.M. she fainted in the bathroom after a feeling of weakness. At this time the blood pressure was 110/60 and the pulse was 80 per minute. The abdomen was diffusely tender and rebound tenderness was present in both lower quadrants. The hematocrit was 34 volumes per cent.

Four hours later under general anesthesia a bimanual examination confirmed a doughlike mass 3 by 3 cm. in the left adnexa. A colpocentesis was performed and a very small amount of fresh blood was obtained which clotted. As preparation was made for a laparotomy, a discoloration of the skin about the umbilicus (Cullen's sign) was noted. On opening the abdomen about 600 c.c. of old blood and clots were found and measured.

The uterus was at the upper limits of normal size and in the midline. The right adnexa were normal. On the surface of the left ovary a 1 by 3 by 4 cm. mass of clotted blood was present, closely adherent to the ovary. The left Fallopian tube was intact and normal without hyperemia. The blood clot was resected from the left ovary but because of continued oozing the remainder of the ovary had to be removed. On cut section the ovary contained a large corpus luteum with an area which appeared to be the point of rupture. The diagnosis at operation was ruptured corpus luteum cyst. The patient was given 500 ml. of whole blood during the operation. The postoperative course was uneventful, and she was discharged on the tenth postoperative day in good condition.

Fig. 1.

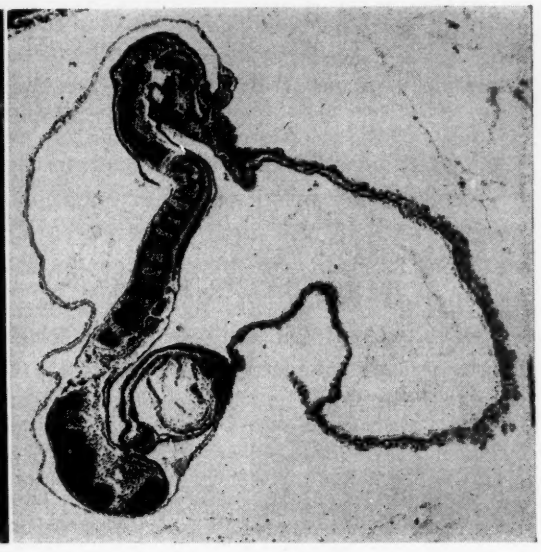


Fig. 2.

Fig. 1.—The ovary with a large corpus luteum showing superficial hemorrhage attached to the surface of the ovary. In the region of hemorrhage, there is a thin irregular layer of trophoblast, showing early differentiation into Langhans' and syncytial cells. Some of these cells have become detached from the ovarian surface.

Fig. 2.—A higher power showing the attached chorionic vesicle which is complete. It also contains an embryo which is about 13 somites. This is a remarkably well-preserved embryo.

This case was first presented at the weekly staff conference as a hemorrhage from a ruptured corpus luteum cyst but after additional sections had been cut the true diagnosis was established. It is reported because of the very fortunate microscopic sections of a remarkably well-preserved thirteen somite embryo implanted on the surface of the ovary.

I am indebted to Dr. William J. Dieckmann for permission to report this case.

SICKLE-CELL ANEMIA: CASE REPORT OF SUCCESSFUL DELIVERY AFTER SIX PREVIOUS UNSUCCESSFUL PREGNANCIES

MORTIMER S. WEINSTEIN, M.D., NORMAN B. JUSKOWITZ, M.D., AND EMANUEL S. COHEN, M.D., NEW YORK, N. Y.

(From the Departments of Obstetrics, Gynecology, and Hematology of the Jewish Memorial Hospital)

RECENT reviews of the literature dealing with the problem of sickle-cell anemia in pregnancy have all pointed to the inherent danger to the mother and to the poor fetal salvage.[1, 2, 3] Anderson and Busby show a maternal mortality of 15.9 per cent and a fetal mortality of 33⅓ per cent in 44 reported cases.[1]

We present the following case report in order to describe a method of treatment which achieved successful delivery in a patient with sickle-cell anemia, who had had six previous unsuccessful pregnancies.

Case Report

Mrs. D. B. (J. M. H. No. 94571), a 26-year-old Negro woman, was seen in the prenatal clinic of the Jewish Memorial Hospital on July 20, 1951. She had had six previous pregnancies which had all ended without a living child. Her last menstrual period was on May 29, 1951, and her expected date of confinement was Feb. 4, 1952. The patient was known to have sickle-cell anemia.

Her previous pregnancies ended as follows:

1. 1945: Vaginal delivery of stillborn fetus at 8 months' gestation.
2. 1947: Spontaneous abortion at 3½ months.
3. 1948: Spontaneous abortion at 3½ months.
4. 1949: Vaginal delivery of stillborn fetus at 7 months' gestation. Patient received 2,500 c.c. of whole blood, post partum.
5. 1950: Vaginal delivery of stillborn fetus at 7 months' gestation.
6. 1950: Vaginal delivery of stillborn fetus at 6 months' gestation. Patient had a substitution transfusion using 9,500 c.c. of whole blood one week prior to delivery. (This was done in an effort to halt a crisis, and also to determine if the chances of fetal survival could be increased. However, on delivery, the condition of the fetus was such that it was apparent that the transfusion was performed after fetal death.)

Physical examination at the time of the first prenatal visit on July 20, 1951, revealed a well-developed, well-nourished Negro woman. The head and chest were negative; no cardiac murmurs were heard; the abdomen was soft; the liver, spleen, and kidneys were not palpable. Vaginal examination revealed a parous introitus; the cervix was clean with old healed lacerations; the uterus was anterior, mobile, soft, and enlarged to twice normal size; the adnexa were negative. There was no evidence of tibial scars. Blood pressure was 120/60; the urine concentrated to 1.020 and the sediment contained no abnormal constituents; there was no sugar or albumin. Examination revealed that the blood was type O, Rh positive, with a negative Kahn test. The red blood count was 2.54 million, the

hemoglobin was 7.8 Gm.; the white blood count was 10,300 with 60 per cent polymorphonuclear leukocytes, 2 per cent eosinophils, 30 per cent lymphocytes, and 2 per cent monocytes. Sickling was noted. There was hypochromia, marked anisocytosis, and poikilocytosis.

Course.—The patient was observed weekly in the prenatal clinic and seen by the hematologist at the same time. She was placed on multivitamins and hematinics; the hemoglobin was checked once or twice each week. She was also given instructions to report to the hospital as soon as any symptoms of crisis or infection developed.

On Aug. 31, 1951, she was given 500 c.c. of compatible blood, and again on Oct. 3, 1951, and Nov. 2, 1951. On Dec. 19, 1951, she developed an upper respiratory infection and was admitted to the hospital. She received antibiotic therapy, and while in the hospital there was a drop in hemoglobin to 7 Gm. She received 1,000 c.c. of whole blood and was discharged on Dec. 27, 1951. The patient was readmitted on Jan. 8, 1952, and given three separate transfusions of 500 c.c. of whole blood because of mild crises as evidenced by a sudden drop in hemoglobin to below 8 Gm. She was discharged on Jan. 12, 1952, to the prenatal clinic. Blood pressure and urine were always normal and her weight gain was limited to 17 pounds. The uterus enlarged normally and the fetus remained active. No edema was present.

The patient was readmitted on Feb. 1, 1952, because of lower abdominal cramps. Examination revealed these to be painful Braxton-Hicks contractions. The uterus was enlarged to term. There was a vertex presentation and the head was unengaged. The fetal heart was 140 in the left lower quadrant and of good quality. Rectal examination revealed an empty pelvis with a closed and uneffaced cervix. The hemoglobin at this time was 10 Gm. Because of the proximity of the expected delivery date, it was decided to keep the patient in the hospital. X-ray pelvimetry on Feb. 3, 1952, revealed a small gynecoid pelvis with a true conjugate of 9.5 cm. and a transverse diameter of the inlet of 10.5 cm. The fetus presented as an unengaged vertex with an extended head. The average diameter of the head was estimated at 9.5 cm. The baby was estimated to weigh 5 pounds. Repeated blood counts were taken and on Feb. 11, 1952, the hemoglobin was found to have dropped to 7.4 Gm. from a previous level of 9.8 Gm. Because the fetal head remained unengaged and could not be impressed into the pelvis, it was decided to perform a cesarean section. Accordingly, a low-flap transverse cesarean section was performed under local anesthesia (1 per cent procaine) with delivery of a normal, living, male child who weighed 6 pounds, 2 ounces. Intravenous Pentothal was used following the delivery of the baby, and the patient received 1,000 c.c. of compatible whole blood during and following the operation. The placenta was normal on gross and microscopic examination. There was no evidence of sicklemia in the child at birth.

The postoperative course was uneventful and the patient's hemoglobin remained at 9 Gm. She was discharged to the outpatient department on the tenth postoperative day.

Follow-up in the immediate postpartum period revealed the mother to be in continued good health without evidence of crisis. Six months later, however, the mother was found to have active sickling with a hemoglobin level of 30 per cent. The baby was in good health and showed no evidence of sickle-cell disease. A complete blood count, sickling preparation, reticulocyte count, and saline fragility test were all within normal limits.

Comment

The high maternal mortality and the poor fetal salvage associated with sickle-cell anemia and pregnancy make the combination a very dangerous one. Fouché and Switzer[3] state that "pregnancy is a severe additional strain. . . . It is possible that a previously mild but active form of the disease which had been unnoticed becomes symptomatic in the presence of the added burden of pregnancy." These authors recommend consideration of therapeutic abortion

in the early stages of pregnancy, and induction of labor as soon as the fetus is viable. Beacham,[2] in his review of the literature, noted that one-third of the cases reported in the literature resulted in stillbirths.

Women with sickle-cell anemia should be forewarned of the possible results before undertaking pregnancy. Once pregnancy has been entered upon, the patient must be placed under careful and constant observation during the entire prenatal course.[1] The patient's blood must be studied at least twice weekly and, in addition, at the time of any subjective symptoms suggestive of a crisis. The hemoglobin must be maintained at a minimum of 8 Gm. during the entire pregnancy. Any drop below this level should be treated immediately with transfusions and by positive pressure oxygen, as levels below 8 Gm. tend to result in fetal anoxia and consequent fetal death. The patient should be kept in the best possible nutritional state. Intercurrent infections should be treated immediately and vigorously. This will help to avoid one of the common causes of crises.

Cesarean section should be reserved for obstetrical complications. Labor should be induced in an attempt to avoid the further subjection of the fetus to the dangers of anoxia, and of the mother to that of crisis, if the following are present: (1) the patient is near term; (2) the size of the fetus permits; and (3) optimum conditions exist (ripe cervix and lack of disproportion).

Conclusions

A case of sickle-cell anemia complicated by pregnancy in a para 0, gravida vii, with a resulting live baby is presented.

If adequate facilities for constant, close observation and treatment are available, including multiple transfusions, throughout the course of pregnancy,[4] there is reason to hope that fetal salvage can be increased and the maternal mortality reduced.

Addendum.—Since this paper was written, this patient was delivered of a normal living full-term female child that weighed 6 pounds, 8 ounces, on Oct. 6, 1953. The patient had a repeat elective cesarean section, at which time a tubal ligation was performed. Both mother and child are doing well.

References

1. Anderson, G. W., and Busby, T.: Am. J. Obst. & Gynec. 58: 75, 1949.
2. Beacham, W. D., and Beacham, D. W.: Obst. & Gynec. Surv. 6: 45, 1951.
3. Fouché, H. H., and Switzer, P. K.: Am. J. Obst. & Gynec. 58: 468, 1949.
4. Spivack, M.: Am. J. Obst. & Gynec. 50: 442, 1945.

GRANULAR-CELL MYOBLASTOMA OF THE VULVA

THOMAS F. SULLIVAN, M.D., JOHN MALFETANO, M.D., AND MEMOIR R. MARSH, M.D., BROOKLYN, N. Y.

(From the Departments of Obstetrics and Gynecology and Pathology, State University of New York at New York City College of Medicine and The Kings County Hospital)

MORE than 300 cases of granular-cell myoblastoma have appeared in the literature. Of these only 7 were found in the female genitals. Geschickter[1] reported the first myoblastoma of the vagina in 1934 and von Szathmary[2] described a second one of the vulva in 1937. Powell,[3] in 1946, had an unusual case with multiple sites of involvement including both ovaries, vulva, and perineum. Tamis,[4] Murphy,[5] Kern,[6] and Valentine[7] added the other 4 genital lesions.

The term "granular-cell myoblastoma" has been credited to Abrikossoff,[8] who described this tumor in 1926 as a "myoblastenomyoma," although other authors including Weber,[10] as far back as 1854, had described similar tumors. Since 1926 numerous papers have been written dealing mainly with the problems of histogenesis and malignancy. The usual sites for this growth are skin, tongue, breast, and respiratory tract. These tumors have been discovered most frequently in the third, fourth, and fifth decades of life, but in a series of 179 cases Murphy reported a 10.6 per cent incidence in the newborn. In a review of the literature it is seen that many of the patients had the lesions present for many years without any apparent harmful effect.

Grossly the lesion is usually small, 1 to 2 cm. in diameter, firm and nontender, and may be pedunculated or sessile. The surface is usually intact. The cut surface is homogeneous, and dull white to tan in color. Histologically it consists of sheets or cords of large polyhedral cells having a poorly defined cell membrane, with a small amount of intercellular connective tissue. They are distributed widely throughout the corium and extend from the papillary layer to the subcutis. The cell is distinguished by the presence of an abundant acidophilic granular cytoplasm. The nuclei are small, round or oval, and centrally placed in the cell. Fat and mucin are absent. The granular cytoplasm stains purple with phosphotungstic acid hematoxylin. In approximately 50 per cent of these tumors marked proliferation of the overlying epidermis is present. This pseudoepitheliomatous hyperplasia has at times erroneously been interpreted as squamous-cell carcinoma.

The histogenesis of this entity has centered about two main hypotheses. The first was proposed by Abrikossoff[8, 9] in 1926, who believed that these tumors are true neoplasms, composed of the precursor cells of striated muscle, arising by a degeneration-regeneration process from adult muscle fibers. This theory was modified by Klinge[11] so as to include a myoblastoma in the skin where no striated muscle was found. This resulted in the dysontogenetic theory, whereby

these tumors would arise from heterotropic rests of embryonic striated muscle. This, in line with Cohnheim's tumor theory, would be the result of incomplete separation of the myotome into the corium and skeletal muscle with the primordial muscle cells being abnormally placed in the cutis. The granular myoblasts of these lesions are similar to those seen in a teratoma of the ovary which contains myoblasts and adult striated muscle elements.

Fig. 1.

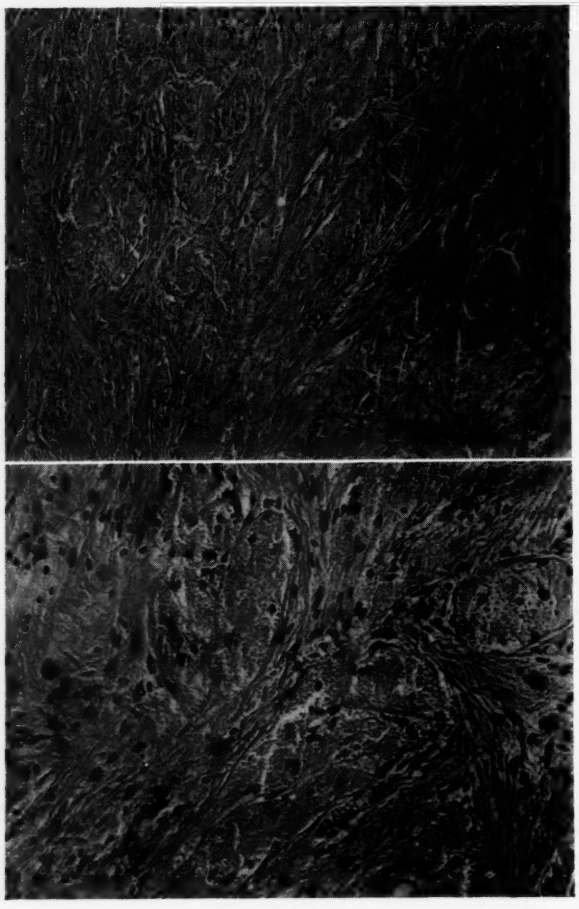


Fig. 2.

Fig. 1.—Field showing typical sheets of large granular cells from specimen of tumor reported in this case. (×150. Reduced one-fifth.)

Fig. 2.—High-power projection of same field as shown in Fig. 1. (×250. Reduced one-fifth.)

In 1939, Leroux and Delarue[12] presented the third histogenic hypothesis. They proposed that the granular cells were mesenchymal cells of histiocytic type containing an unknown substance. Ringertz,[13] in 1942, agreed that these tumors were of mesenchymal origin and that they contained the products of protein breakdown. This storage tumor hypothesis must await confirmation or condemnation by biochemical studies not as yet completed.

Most investigators, including Klemperer,[14] believed that these tumors arose from misplaced primitive myoblasts in accordance with Klinge's theory. In the past few years evidence has been presented to suggest that peripheral nerve might be the tissue of origin. Fust and Custer,[15] who demonstrated concentric masses of granular tumor cells with cores consisting of bundles of axis cylinders, proposed the term "granular-cell neuroblastoma" to replace the entity now called granular-cell myoblastoma. Ashburn and Rodger[16] supported this concept with similar findings in six cases.

As to malignancy, a great majority of granular-cell myoblastomas are benign altogether. Malignant forms have been reported by von Meyenburg[17] and Ravich and associates.[18] Dockerty[19] reported a malignant myoblastoma of the vulva which has not been accepted since the original lesion was not examined histologically and recurrences displayed sufficient sarcomatous changes to place the original type of tumor in doubt.

Case Report

M. S., a 23-year-old married Negro woman, para 0, gravida 0, reported to the gynecologic clinic of the outpatient department on Nov. 24, 1952, complaining of a swelling on the right labium. The patient was 16 weeks pregnant. She stated the mass had been present for 22 years. It was not painful and had not changed its size for at least ten years.

Physical findings were negative except for the presence of a four months' intrauterine gestation and a hard 3 by 2 cm. raised area on the superior third of the right labium majus which was nontender. The skin was intact over the raised area. On Nov. 28, 1952, under local anesthesia, a 2 by 3 cm. hard mass was excised by sharp dissection. The mass appeared well encapsulated and gray white in color. When the patient was last seen on May 5, 1953, there was no evidence of recurrence.

Pathological Findings.—The specimen was a small oval-shaped piece of tissue measuring 3 by 2 cm., firm and gray white in color. Sections (Figs. 1 and 2) revealed scattered sheets of large polyhedral cells with a moderate amount of fibrillar intercellular connective tissue. The individual cells had a poorly defined cell membrane. Their cytoplasm was granular and the nuclei were small, round, and centrally located. The nuclei stained hyperchromatically. There were no mitoses noted. No epithelium was present.

Diagnosis: Granular-cell myoblastoma, uniform type.

Summary

A review of the literature revealed over 300 cases of granular-cell myoblastomas of which only 7 were found on the female genitals. Another case has been added to this small series of genital granular-cell myoblastomas. The various theories on the histogenesis of this entity have been reviewed.

References

1. Geschickter, C. F.: Am. J. Cancer **22**: 378, 1934.
2. von Szathmary, A.: Magyar orvosi arch. **38**: 260, 1937.
3. Powell, E. B.: Arch. Path. **42**: 517, 1946.
4. Tamis, A. B., and Kowles, J. J.: Am. J. Obst. & Gynec. **42**: 543, 1941.
5. Murphy, G. H., Dockerty, M. B., and Broders, A. C.: Am. J. Path. **25**: 1157, 1949.
6. Kern, A. B.: Arch. Dermat. & Syph. **62**: 109, 1950.
7. Valentine, F. M., and Thomas, J. R.: Am. J. Obst. & Gynec. **65**: 213, 1953.
8. Abrikossoff, A. J.: Virchows Arch. f. path. Anat. **260**: 215, 1926.
9. Abrikossoff, A. J.: Virchows Arch. f. path. Anat. **280**: 723, 1931.
10. Weber, C. O.: Virchows Arch. f. path. Anat. **7**: 115, 1854.

11. Klinge, G.: Verhandl. d. deutsch. path. Gesellsch. **23**: 376, 1928.
12. Leroux, R., and Delarue, J.: Bull. Assoc. franç. p. l'é'tude du cancer **28**: 427, 1939.
13. Ringertz, N.: Acta path. et microbiol. Scandinav. **19**: 112, 1942.
14. Klemperer, P.: Am. J. Cancer **20**: 324, 1934.
15. Fust, J. A., and Custer, R. P.: Am. J. Clin. Path. **19**: 522, 1949.
16. Ashburn, L. I., and Rodger, R. C.: Am. J. Clin. Path. **22**: 440, 1952.
17. von Meyenburg, H.: In Henke, F., and Lubarsch, O., editors: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, 1929, Julius Springer, p. 468.
18. Ravich, A., Stout, A. P., and Ravich, R. A.: Ann. Surg. **121**: 361, 1945.
19. Dockerty, M. B., and Sadler, W. P.: AM. J. OBST. & GYNEC. **61**: 1047, 1951.

451 CLARKSON AVENUE

SPHEROCYTOSIS AS A MANIFESTATION OF POSTABORTAL CLOSTRIDIUM WELCHII INFECTIONS

G. Gordon Hadley, M.D., and Richard D. Ekroth, M.D., Los Angeles, Calif.

(From the Departments of Pathology and Obstetrics and Gynecology, College of Medical Evangelists)

A SEVERE complication of abortion is infection by *Clostridium welchii,* the "gas bacillus." The organism is frequently isolated as a saprophyte from the female genital tract in both antenatal and postpartum cases.[1, 2] Under the proper circumstances of introduction into dead and devitalized tissue the organism may become the causative agent of a severe infection involving the products of conception, the uterus, and the blood stream. Of puerperal infections with this organism, 60 to 75 per cent are said to be postabortal.[3] The infection, though often severe and fatal, is by no means always so, and numerous cases of recovery are reported, in many of which antibiotics and other therapeutic measures were used.[2-6]

The typical picture of a severe infection is that of an acutely ill individual with evidences of toxemia and severe intravascular hemolysis giving a triad of a yellow-brown discoloration of the skin, burgundy red serum, and a dark red discoloration of the urine. The patient who lives through this stage will enter next a period of anuria similar to that in any other hemoglobinuric nephrosis.

Spherocytosis, the subject under discussion in this report, refers to the presence in the blood of spherocytes, or microspherocytes as they are also called. As compared to normal erythrocytes these red cells appear to be smaller and to stain more intensely without the usual pallor in the center. These staining qualities are due to the increased thickness of the cell and this abnormal shape is also responsible for the increased hemolysis in the osmotic fragility tests. Though typically seen in congenital hemolytic jaundice, they are found in other conditions.

Although spherocytes may be produced by hemolytic toxins and antibodies, a search of a number of articles dealing with postabortal *Clostridium welchii* infection failed to reveal any discussion of the subject except for an apparent passing mention in three papers.[7, 8, 9] In the two cases described in this report spherocytosis was an outstanding finding and in the milder case with recovery it was first noticed in a routine blood count and the case then further studied as a *Clostridium welchii* infection only as a result of this observation.

Case 1.—The patient, Mrs. N. H., was a 20-year-old Mexican woman, admitted to the hospital Oct. 16, 1951. The last menstrual period was Aug. 16, 1951. One week before entry she had a catheter inserted into the uterus which was followed by bleeding which

later stopped. The night before entry she apparently again inserted the catheter. Bleeding occurred afterward, along with sharp intermittent pains which became progressively worse. Upon entry she was passing red urine and had had chills.

Upon entry, the hemoglobin was 8.6 Gm. per 100 ml. The red blood count was 2,630,000; the white blood count 39,900, with 75 segmented neutrophils and 19 band forms. A large number of the cells as seen on stained smear were spherocytes (Fig. 1). A catheterized specimen was grossly quite red. A Gram stain of a cervical smear showed numerous gram-positive bacilli. A guinea pig used for the Welch-Nuttall test was definitely positive when observed after about nine hours of incubation. Typical stormy fermentation of milk was also obtained, as was characteristic gas formation on cooked meat media. A total hysterectomy was done. The abdominal wound oozed after surgery, and a culture of this was positive on cooked meat and litmus milk media. Serum hemoglobin on Oct. 17, 1951, was 175 mg. per 100 ml. Later in the day it was 300 mg. per 100 ml. On Oct. 19, 1951, it was 204 mg. per 100 ml.

Her urinary output shut down and the serum potassium progressively rose and varied from 5.6 to 8.2 meq. per liter. Serum hemoglobin dropped progressively and was 90 mg. per 100 ml. on Oct. 23, 1951. Nonprotein nitrogen rose to 270 mg. per 100 ml. on Oct. 23, 1951, and the patient died Oct. 24, 1951.

The main pathology at autopsy centered about the kidneys which showed a marked hemoglobinuric (lower nephron) nephrosis with many of the tubules plugged with granular hemoglobin casts.

CASE 2.—The patient, Mrs. W. C., a 25-year-old Negro woman, was admitted to the hospital May 10, 1952, two weeks after having gone home following an exploratory laparotomy at which the appendix was removed, and an adhesion freed. At that time it had been noted that she had an intrauterine pregnancy of about two and one-half months. This had been left undisturbed.

On entry, May 10, 1952, she complained of abdominal cramping for two days and vaginal bleeding since early that morning. Physical examination revealed blood clots in the vagina and an acutely tender abdomen. The abdominal scar showed no inflammation and the clinical impression was that of a threatened abortion. At that time the patient denied any instrumentation, but later admitted having made an attempt at abortion using an enema tip and goose quill.

On the day of entry her temperature went as high as 103.2° F. The following day the temperature was only 99.8° F. at peak, and from then on she was relatively afebrile. Her blood count on admission showed a hemoglobin of 11.4 Gm. per 100 ml. The red blood count was 3,820,000 per cubic millimeter, and the white blood count 12,300, with 95 per cent neutrophils. No abnormal red cells could be seen in the stained smear. A blood study two days later showed a hemoglobin of 10.4 Gm. per 100 ml., red blood count 3,350,000, and white blood count 30,000 with 89 per cent neutrophils, 20 of which were band forms. Numerous spherocytes were noted. Hemoglobin on May 13, 1952, was 9.5 Gm. per 100 ml. Repeated tests for serum hemoglobin were negative. A Coombs test was negative. A 500 c.c. transfusion was given May 13, 1952. Treatment while in the hospital consisted of penicillin and streptomycin in addition to other supportive measures. Hemoglobin thereafter increased somewhat and spherocytes decreased. The patient was sent home May 20, 1952, feeling well.

Material passed per vaginam on May 12, 1952, was triturated under sterile conditions and injected into the blood stream of a guinea pig which was sacrificed and incubated. When examined at the end of about 15 hours the animal was greatly distended with gas and had a foamy liver. As in the other case, a smear from the liver was full of large gram-positive bacilli without spores.

A follow-up blood smear taken on July 9, 1952, showed no spherocytes (Fig. 1).

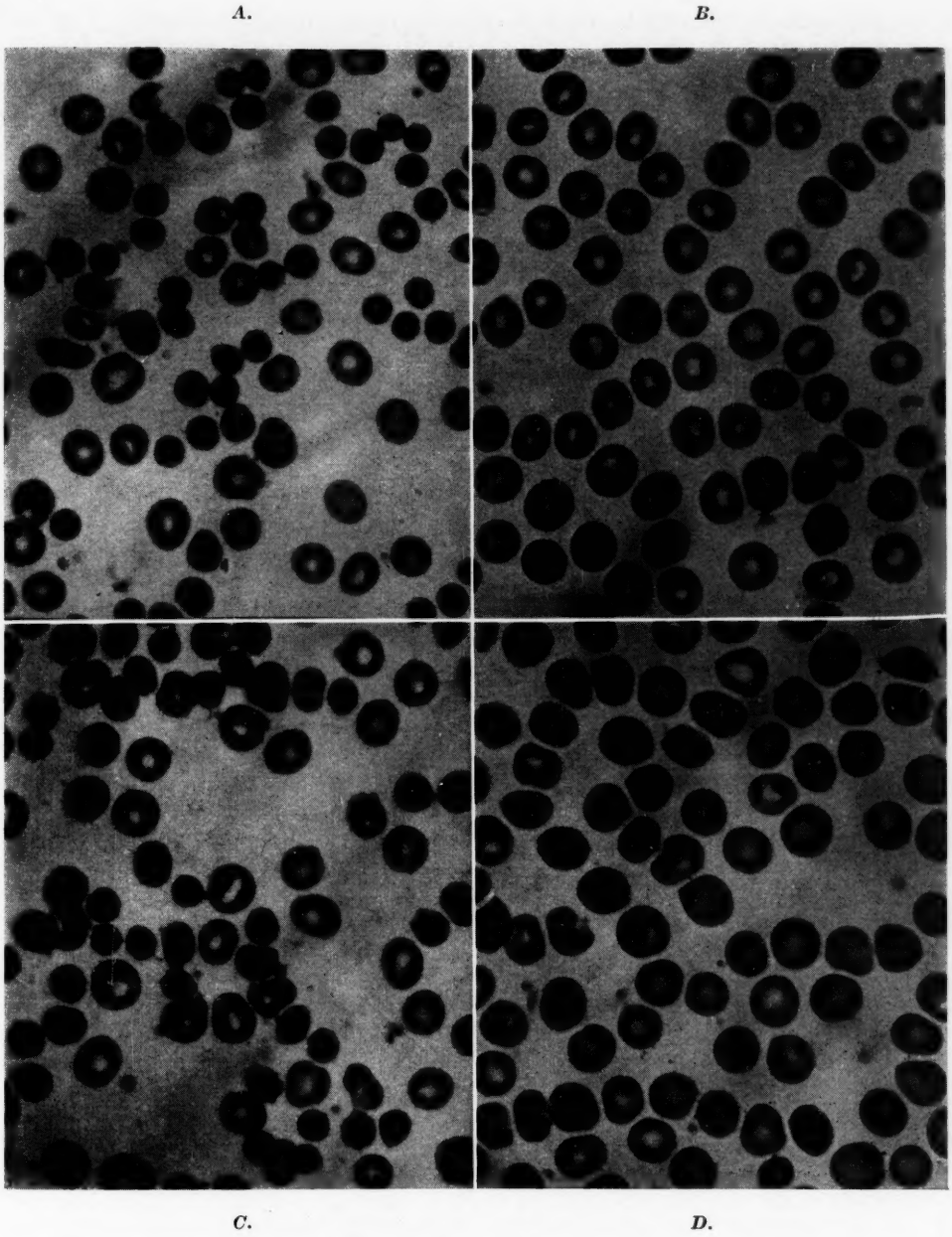


Fig. 1.—*A* (Case 1), Blood smear showing spherocytes.

B (Case 2), Blood smear taken during first hospital admission, showing normal morphology of red cells. April 17, 1952.

C (Case 2), Blood smear taken during admission because of abortion, showing numerous spherocytes.

D (Case 2), Blood smear taken after convalescence showing normal morphology of red cells again.

Summary

Two cases of postabortal *Clostridium welchii* infection are presented, both of which showed spherocytosis as an outstanding finding. In the patient who recovered, differential smears before and after illness showed normal morphology

of the red cells in contrast to marked spherocytosis during the illness. The toxins produced by the organism were apparently not severe enough to cause hemolysis as was true in the fatal case. Evidence presented by the case with recovery seems to indicate that careful observation of the differential smears might well be the first finding of postabortal and other *Clostridium welchii* infections.

References

1. Salm, R.: J. Obst. & Gynaec. Brit. Emp. **51**: 121, 1944.
2. Falls, F. H.: Am. J. Obst. & Gynec. **25**: 280, 1933.
3. Sadusk, J. F., Jr., and Manahan, C. P.: J. A. M. A. **113**: 14, 1939.
4. Bigby, M. A. M., and Jones, F. A.: J. Obst. & Gynaec. Brit. Emp. **56**: 636, 1949.
5. Dietel, H.: Geburtsh. u. Frauenh. **10**: 418, 1950.
6. Hudson, G. S., and Rucker, M. P.: Am. J. Obst. & Gynec. **50**: 452, 1945.
7. Natale, A. M., Grichener, E., and Picena, J. P.: Rev. Asoc. méd. argent. **58**: 195, 1944.
8. Inda, F. F., Da Rin, C., and Lefevre, H.: Semana méd. **1**: 385, 1942.
9. Sicard, A., Dufourmentel, C., and Agopian, K.: Mém. Acad. de chir. **75**: 495, 1949.

312 North Boyle Avenue

Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Selected Abstracts

Anesthesia, Analgesia

Klink, Edward Walter: Perineal Nerve Block—An Anatomic and Clinical Study in the Female, Obst. & Gynec. 1: 137, 1953.

The sensory innervation of the vagina and perineum was studied by dissection of the sacral nerves on 85 cadavers, and by observation of anesthesia produced when specific nerve roots were injected with an anesthetic agent. To confirm the anatomical and clinical studies more than 300 perineal nerve blocks were performed in obstetrical and gynecological patients.

It was found that the pudental nerve innervates the lower vagina and the whole of the perineum, including the clitoris, the labia, and the entire perineal body. It was noted that the inferior hemorrhoidal nerve was a branch of the pudendal nerve in 50 per cent of the dissections, and in the other 50 per cent it began as a separate branch of the fourth sacral nerve. As a result of this study a technique for producing perineal anesthesia is presented. This consists of injecting 10 c.c. in equally divided amounts in three different areas in the pudendal canal, so that the pudendal nerve, the inferior hemorrhoidal, and the posterior femoral cutaneous nerve are blocked. One per cent Xylocaine without the addition of vasoconstrictor agents or hyaluronidase was used as the anesthetic agent. The clinical use of this method of anesthesia is discussed in carefully selected cases. It is satisfactory for spontaneous as well as forceps deliveries, for the performance and repair of episiotomies, and for breech deliveries. It is of particular value where it is necessary to avoid increased anoxia to the fetus. Pudendal block may also be used for bartholinectomy, biopsy of the vulva, and simple vulvectomy. The question of drug sensitivity is briefly presented. Eleven excellent drawings are used to illustrate the anatomical studies and the technique of injection.

ARTHUR V. GREELEY

Leighton, Herbert T., and Hershenson, Bert B.: "Spinal" Headache, Obst. & Gynec. 1: 426, 1953.

A study of "spinal" headache in 404 patients in whom spinal anesthesia was used for vaginal delivery is presented. The incidence of headache in the 235 untreated patients was 26 per cent in contrast to an incidence of 3.4 per cent in a group of 176 patients treated by the application of epigastric pressure, by means of a specially constructed belt. The causes of "spinal" headache are discussed.

ELMER E. KRAMER

Cancer, Malignancies

Schinz, N. R., and Uehlinger, E.: Comparative Studies of Atypical Epithelium of Carcinoma in Situ and Macroscopic Carcinoma of the Cervix Uteri, Gynaecologia 134: 146, 1952.

In making comparative studies of exfoliated epithelial cells from carcinoma in situ and exfoliated cells of true macroscopic cancer, certain criteria were established. Diagnosis of carcinoma in situ was made solely on the biopsy studies, using multiple serial sec-

tions of the lesion to certify that the pathology was localized and had not spread. Diagnosis of macroscopic invasive cancer was made by combined biopsy studies together with evidences of gross spread to other tissues and organs. Criteria for diagnosis of carcinoma on the stained smear are the same as those outlined by Papanicolaou and consist of anaplasia, hyperchromaticism, atypical cytoplasm, and all other abnormalities so frequently described. The authors, by means of text and diagrams, illustrate how normal and abnormal exfoliation of cells occurs and how then cytological changes are demonstrated by means of the smear technique. As the result of their studies they find no difference in the type of smear produced by "in situ" and by Stage I to Stage IV carcinomas.

L. B. WINKELSTEIN

Vetter, Hans: Early Diagnosis of Cervical Cancer, Gynaecologia **134**: 154, 1952.

Tremendous advances have been made in the last two decades in the early diagnosis of carcinoma of the cervix uteri. This is especially noteworthy because the earlier the diagnosis, the easier the treatment, and also because the percentage of cures is directly proportional to the degree of containment of the disorder. The author has, over a period of twenty years, made multitudinous studies of large numbers of cervices. For this study he has utilized the Hinselmann colposcope. This is an optical enlarging instrument, functioning similarly to a microscope, which allows the observer to examine directly, in vivo, the changes in the epithelium of the cervix. The author describes the appearance of the normal cervical surface and also the abnormal changes which he has observed. Cytological variations in the epithelium similar to those observed in actual carcinoma have been observed as early as 12 to 20 years before the actual development of a demonstrable malignancy. All observations were correlated with biopsy studies, as well as with the cytological smear analysis of Papanicolaou. The author feels that colposcopy is an excellent method, not only for the demonstration of cancer itself, but also for continuous observation of suspicious lesions.

L. B. WINKELSTEIN

Gynecology

Borell, Ulf: The Distribution of Organic and Inorganic Phosphate in Human Endometrium Under Normal and Pathological Conditions, Acta obst. et gynec. Scandinav. **32**: 170, 1953.

Endometria of patients with normal menses, with menopausal status, and with menstrual disturbances of various types were extracted, and the amounts of orthophosphate, easily hydrolyzable and slowly hydrolyzable phosphate in each group were determined. The content of phosphate compounds was greater in differentiative-phase endometria than in proliferative-phase specimens in the group with normal menstrual histories. Just before the onset of menstruation, the amount of free phosphate was found to be higher at the expense of the slowly hydrolyzable fraction. In endometria of postmenopausal women and of women with menstrual disturbances, the residual phosphate proportion was greater than that of the other organic phosphates determined. Administration of estradiol benzoate produced an increase in the amounts of orthophosphate and lipid phosphate; if progesterone was subsequently administered, the resulting endometria showed an increase in the quantity of slowly hydrolyzable phosphate. Borell believes that this evidence supports the concept that progesterone is produced to some extent during the proliferative phase of the menstrual cycle, and is not limited to the differentiative phase. His studies also lead him to propose that the endometrium is under the sole influence of estrogenic hormone just prior to the onset of menstruation.

DOUGLAS M. HAYNES

Langely, F. A., Smith, J. P., and Woodcock, A. S.: Debatable Uterine Tumors, Acta obst. et gynec. Scandinav. **32**: 143, 1953.

Four unusual and morphologically dissimilar tumors of the uterus are described to illustrate the usefulness of the embryological approach to tumor histogenesis. Two rare

endometrial lesions, a pure sarcoma and a carcino-sarcoma, may be explained histogenetically by taking cognizance of Gruenwald's demonstration that, in man, the celomic (and therefore mesenchymal) Müllerian ducts which give rise to the uterus also produce for a time the nonepithelial tissue of the uterovaginal canal. For this reason, it is not surprising that aberrant neoplastic proliferation of endometrial epithelium may form both epithelial and mesenchymal tissue reproductions. This concept is not to be confused with the differentiation of endometrial epithelium from stroma, which is a late development, occurring normally in the postmentstrual regenerative phase.

The other two lesions described, an example of so-called "stromal endometriosis" and one of agranulosa-like tumor arising in the uterine wall, are also rendered histogenetically simpler by applications of Gruenwald's hypothesis. Stromal endometriosis may be explained on the assumption that Müllerian tissue retains its differentiating potentiality in the adult. The presence of an ovarian type of neoplasm arising primarily in the uterus may be explained by the invocation of embryological evidence that both uterus and ovary are derived from the same mesenchymal anlage.

The authors are careful to point out that these embryological avenues of approach to "debatable" uterine tumors are reasonable means of explaining otherwise bizarre histologic findings, but they are not sufficiently unequivocal to warrant a system of classification of such tumors constructed purely on Gruenwald's hypothesis.

DOUGLAS M. HAYNES

Appelberg, Gustaf: Two Cases of Cystadenomyofibrosis Cystica Cervicis Uteri, Acta obst. et gynec. Scandinav. **32:** 229, 1953.

The term "cystadenomyofibrosis cystica cervicis uteri" has been used to designate the rare occurrence of a pronounced downgrowth of cervical mucosa into the deep layers of the myometrium of the cervix with subsequent development of large glandular cystic spaces in what is to be considered an ectopic location. Although the epithelium of the displaced and distended glands is compressed and atrophic, its mucus-production potential is retained, and it is histologically well differentiated. The epithelial character is usually that of normal cervical epithelium, but may sometimes reproduce that of the corporal endometrium. This entity is considered histogenetically separate from cervical endometriosis, and is clinically relatively asymptomatic as compared with that condition. The recognition of cervical cystadenomyofibrosis is important because it is readily confused with mucus-producing adenocarcinoma of the cervix.

Appelberg presents two case reports of patients with this lesion observed in 1951 in the Radiological Clinic in Lund, Sweden. Both patients had received stilbestrol for minor preclimacteric symptoms, and one had an episode of severe uterine bleeding. Both were treated by total hysterectomy and bilateral salpingo-oophorectomy, and were found to have multiple follicular ovarian cysts in addition to the cervical lesion. Robert Meyer thought that this lesion was related etiologically to chronic inflammation and cervical trauma, but these features were absent in Appelberg's two patients, aside from minor cystic cervicitis. The diagnosis was made in one case by fractional curettage at the time of hemostatic dilatation and curettage for metrorrhagia; in the second case, hysterectomy was done because of the bimanual palpation of acystic ovarian mass, and the diagnosis of cystadenomyofibrosis cystica was made from the study of the operative specimen.

DOUGLAS M. HAYNES

Rinvik, Roald: Granulosa-Cell Tumor in a Case of Precocious Puberty, Acta obst. et gynec. Scandinav. **32:** 222, 1953.

The author reports the case of a 4-year-old girl with precocious puberty which resulted from a large (1,000 Gm.) granulosa-cell tumor. The patient presented severe mesenteric lymphadenopathy and rapidly developing ascites. The urine contained increased quantities of estrogenic fractions and 17-ketosteroids. The latter finding is interpreted as

a possible indication of coexistent adrenal disease, or, alternately, an adrenal hyperfunction released via the pituitary adrenocorticotropic hormone following overproduction of estrogen fractions. This adrenal hyperfunction continued after the operation; one year after removal of the tumor, she was considerably taller than the average normal child of her age. The urinary 17-ketosteroids fell to a normal level within 6 weeks of operation, however, even though there was apparently some persistent growth-stimulating mechanism. No satisfactory explanation for the ascites was found, and the suggestion is made that this represented a situation analogous to that encountered in Meigs' syndrome. There was no evidence of recurrence of the tumor in one year, and the stigmas of precocious puberty had disappeared soon after the removal of the tumor.

DOUGLAS M. HAYNES

Newborn

Doxiadis, S. A., Goldfinch, Margaret K., and Cole, Nancy: "Proteinuria" in the Newborn, Lancet p. 1242, Dec. 27, 1952.

Proteinurea has been reported by many as occurring normally in the newborn. This paper describes a current reinvestigation of this subject. Urine specimens collected from male babies were tested for protein, first by acidification with trichloracetic acid (0.1 25 per cent [w/v] to 1 ml. of urine), then by comparison of the turbidity with tubes of standards. If the urine contained more than 15 mg. of protein per 100 ml., urates were removed by saturating the urine with ammonium chloride and adding concentrated ammonium hydroxide (Hopkins method). (This procedure is shown by them not to remove protein from serum free from urate, diluted so as to contain 10 to 100 mg. protein per 100 ml.) After removing the precipitate, the resulting supernatant solution was retested for protein by again acidifying with trichloracetic acid. Of 103 urine specimens from 97 newborn male infants 1 to 21 days of age so tested, 30 specimens, all having a high specific gravity and deep color, all passed in the first 5 days, gave a turbidity with trichloracetic acid when first tested. After removal of urates, the urine from only one infant continued to show a positive test and it was impossible to rule out contamination in this case. The authors summarize by saying, "Proteinurea as a physiological phenomenon in the newborn infant does not exist. The fallacy has arisen from the excessive excretion of urates in the first few days of life, interfering with the test for protein." ROY W. BONSNES

Rumbolz, William L., and McGoogan, Leon S.: Placental Insufficiency and the Small Undernourished Full-Term Infant, Obst. & Gynec. 1: 294, 1953.

Presented are 20 pregnancies which progressed to 36 weeks' gestation, or longer, with delivery of an infant weighing 4 pounds, 8 ounces (2,000 grams) or less, for an incidence of 0.24 per cent. Seven of the pregnancies were complicated by pre-eclampsia or pre-existing hypertensive disease. Uterine growth paralleled the normal until about the thirty-first week when the curve leveled off into an almost straight line. This failure in growth might lead one to suspect this condition although the absolute diagnosis of placental insufficiency and a poorly nourished infant is possible only after delivery of the child and examination of the placenta. A study of the placentas revealed 19 to have infarcts varying in size and extent. The over-all fetal mortality was 45 per cent.

It is recommended that labor be conducted in principle as in the expected premature infant, with little or no sedation, close observation of the fetal heart, oxygen inhalation, and delivery under conduction-type anesthesia. ELMER E. KRAMER

Pregnancy, Complications

Studdiford, William E., and Decker, Wayne H.: Management of Premature Separation of the Placenta, Obst. & Gynec. 1: 418, 1953.

Presented are 305 patients with premature separation of the normally implanted placenta observed at the Bellevue Hospital from 1941 through 1951. During the period 25,030

patients were delivered, giving an incidence of 1:82 deliveries. The degree of separation is classified as (1) minor, in the presence of a living fetus; (2) intermediate, when the fetus shows signs of embarrassment, and (3) major, when the fetus is dead. Two hundred five cases (66 per cent) were classified as minor, 4 as intermediate, and 96 (33 per cent) as major separations. Study of the patients brought out two important features in the clinical course: (1) major separations occurred in a relatively short period of time, dooming the fetus practically at the onset; (2) in minor separations, evidence indicated that progression of the detachment rarely occurred. Therefore, fetal outcome is almost always predetermined and interference by the obstetrician will do little to alter this. There were two maternal deaths (0.66 per cent) both of which occurred in patients with major separations. The incidence of postpartum hemorrhage was 6.9 per cent, which was judged on objective evidence: fall in blood pressure, pallor, tachycardia. The incidence of cesarean section for premature separation per se was 7.8 per cent. It was felt that the incidence of cesarean section might be reduced without jeopardy to the mother or fetus if a labor of less than 12 hours could be anticipated and shock prevented. Methods employed to encourage and hasten vaginal delivery are described. ELMER E. KRAMER

Radiation

Barter, Robert H., and Parks, John: The Advantages of X-ray Diagnosis in Pregnancy, South. M. J. **46**: 555, 1953.

Improved clinical management of the pregnant patient inevitably results from the more frequent use of x-ray diagnosis. Ideally, all primigravid patients should have the benefit of x-ray pelvimetry. A diagonal conjugate of 11.5 cm. or less or a reduction in the interspinous and intertuberous diameters, or abnormal curvature or forward displacement of the sacrum, all of these are significant findings. Where routine x-ray is not practical the authors advise that every patient with one of the following clinical conditions should be given the benefit of x-ray: primigravid patients with breech presentation, primigravid patients with unengaged head at term, all patients 5 feet or less in height, patients with histories of difficult labor, patients with histories of pelvic fracture.

All patients should have an x-ray before a diagnosis of uterine inertia is made. The antepartum diagnosis of multiple pregnancy can be made only with certainty by x-ray. In the presence of an overdistended uterus, x-ray is important to differentiate polyhydramnios, a single large fetus, or multiple gestation. Fetal anomalies can usually be diagnosed only by x-ray. Fetal deaths in utero can be established in practically all cases on the sixth or seventh day after death. A soft-tissue technique to localize the point of implantation of the placenta is indicated in most patients who have bleeding during the last trimester.

In the discussion of this paper it was emphasized that x-ray examinations of the abdomen and pelvis of the pregnant woman should be limited to the fewest possible exposures because of radiation hazard to the fetus. The hazard is greatly minimized if x-ray evaluation is delayed until after the fifth month of gestation.

WILLIAM BICKERS

Correspondence

Hemorrhage of Maternal or Fetal Origin in Separation of Placenta?

To The Editor:

In his interesting case report entitled, "Intrapartum Hemorrhage From the Cerebral Vessels of an Anencephalic Fetus," published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY **56**: 902, 1953, Dr. Fist opens with the statement, "Intrapartum hemorrhage may be placental, maternal, or fetal in origin. Hemorrhage from the placenta may be due to low implantation, separation of a normally implanted placenta, rupture of a marginal sinus . . . and hemorrhage from vasa previa. Maternal hemorrhage may be due to rupture of genital varicosities (rare), rupture of the uterus, or laceration or erosion into a blood vessel of the cervix."

While it may be quibbling over terminology, I do not believe that this is a correctly stated classification. The bleeding of premature separation, low implantation, or rupture of a marginal sinus is due to varying degrees of separation of the placenta from its normal attachment. But the actual blood loss is from the maternal side of the two circulations which are in juxtaposition at the placental site and not from the placenta itself. In other words, the maternal and not the fetal organism is being exsanguinated.

I proved this to myself with a very simple experiment a few years ago. I had seen several infants die after what seemed to be minor degrees of placental separation, and wondered whether the death of the fetus in these cases occurred from anoxia due to the partial separation of their oxygen-procuring organ, or whether there was some bleeding from the placental site which exsanguinated the infant. In a series of deliveries, I gave Ergotrate, grain $\frac{1}{320}$, intravenously, after the delivery of the anterior shoulder and then waited for a strong uterine contraction to deliver the infant's body. In certain of these cases, the intact placenta would follow immediately and we had the fetus, cord, and placenta delivered intact. In a few of these, the umbilical artery was still actively pulsating at its insertion to the placenta, and we had an entire fetal circulation with blood being pumped out the umbilical artery through the placenta and returning through the veins of the cord. If the maternal surface of the placenta of this preparation was gently wiped dry, it remained dry. If, however, this maternal surface was cut or torn, it bled actively. In other words, if the placenta separates from its attachment, there is no bleeding from the placenta itself as long as it remains intact. If it is torn or injured, blood is lost from the fetal circulation. Hence the bleeding in these placental accidents should be classified as maternal.

Dr. Fist also classified the bleeding of vasa previa as placental. Here the bleeding is from injury to the vessels of the cord as they pass across the cervical os or lower uterine segment on their way to the placenta from their velamentous insertion, and the bleeding is directly from the fetal circulation. Death of the fetus in these cases is from actual exsanguination, and the bleeding should be classified as fetal.

For these reasons, I would suggest revising Dr. Fist's classification of intrapartum hemorrhage somewhat as follows:

Maternal.—Due to (a) Placental accidents.
(b) Rupture of the uterus.
(c) Rupture of maternal varicosities.
(d) Injury to the cervix.

Fetal.—Due to (a) Bleeding from vasa previa.
(b) Bleeding from some fetal injury.

J. E. MORGAN, M.D.

5500 RIDGE ROAD
CLEVELAND 29, OHIO
NOV. 18, 1953